ONCOLOGY

Oncology is the study of cancer. The word comes from the Greek word for *tumor* or *mass.* The medical field of oncology covers cancer research, risk and prevention, diagnosis, treatment, and survivorship.

Specialists trained in oncology provide care for people who are at risk for cancer, being treated for cancer, and living with cancer after treatment. Together, these specialists might be called a cancer care team.

There are specialized areas of oncology care, too. Some examples include:

* Hematology oncology (blood cancers such as leukemia, lymphoma, and multiple myeloma)
* Specific types of cancer (such as breast oncology or gynecology oncology)
* Children with cancer (pediatric oncology)
* Survivorship (post-treatment)

### **Who is an oncologist**

An oncologist is a cancer doctor. These healthcare providers specialize in oncology — the branch of medicine that focuses on diagnosing, staging and treating cancer.

A visit to an oncologist gives you an opportunity to talk with a specialist who understands what you’re going through. Oncologists also have experience in helping people cope with the stress and anxiety a possible cancer diagnosis can bring. They’re ready to help, and they’ll walk with you every step of the way.

## **What does an oncologist do?**

An oncologist is a physician (medical doctor) who specializes in cancer. An oncologist leads a cancer care team in the care of people with cancer. Oncologists may:

* Diagnose cancer
* Make treatment recommendations and create treatment plans
* Carry out or oversee treatment
* Evaluate how the cancer is responding to treatment
* Coordinate a patient’s care with other members of the cancer care team
* Provide follow-up care after treatment is completed
* Conduct research through clinical trials

## **Oncology specialties**

Many oncologists focus on specialty areas based on how cancer is treated:

* Surgical oncologists treat cancer using surgery, including removing the tumor and nearby tissue during an operation. This type of surgeon can also perform certain types of biopsies to help diagnose cancer.
* Medical oncologists treat cancer using medication, including chemotherapy, immunotherapy, and targeted therapy.
* Radiation oncologists treat cancer using radiation therapy, which is the use of high-energy x-rays or other particles to destroy cancer cells.

There are also oncologists who specialize in caring for specific groups of patients or types of cancers. Here are some examples:

* Breast oncologists treat breast cancers in men and women.
* Geriatric oncologists work with people with cancer who are age 65 and older. Older adults can have additional challenges. Geriatric oncologists specialize in providing the best care for older adults.
* Gynecologic oncologists treat cancers in such reproductive organs as the cervix, fallopian tubes, ovaries, uterus, vagina, and vulva.
* Hematologist oncologists treat blood cancers, such as leukemia, lymphoma, and myeloma.
* Neuro-oncologists treat cancers of the brain, spine, and nervous system.
* Pediatric oncologists treat cancer in children and teens. Some types of cancer occur most often in these younger age groups. When these types of cancer occasionally occur in adults, those adult patients may choose to work with a pediatric oncologist.
* Thoracic oncologists treat cancers inside the chest area, including the lungs and esophagus.
* Urologic oncologists treat cancers in the genitourinary system, such as the bladder, kidneys, penis, prostate gland, and testicles.

**COMPREHENSIVE LIST OF DISEASES UNDER ONCOLOGY**

## Carcinomas (Epithelial Cell Cancers)

* Adenocarcinoma (various organs)
* Basal Cell Carcinoma (skin)
* Squamous Cell Carcinoma (skin, lung, head and neck)
* Transitional Cell Carcinoma (urothelial tract)
* Ductal Carcinoma In Situ (breast)
* Invasive Ductal Carcinoma (breast)
* Invasive Lobular Carcinoma (breast)
* Medullary Carcinoma (breast)
* Mucinous Carcinoma (breast, colon)
* Papillary Carcinoma (thyroid, breast)
* Hepatocellular Carcinoma (liver)
* Cholangiocarcinoma (bile duct)
* Lung Cancer (Non-Small Cell, Small Cell)
* Pancreatic Adenocarcinoma
* Gastric (Stomach) Cancer
* Colorectal Cancer (colon, rectal)
* Esophageal Cancer
* Cervical Cancer
* Endometrial (Uterine) Cancer
* Ovarian Cancer (epithelial types)
* Prostate Cancer
* Bladder Cancer
* Renal (Kidney) Cell Carcinoma
* Thyroid Cancer (papillary, follicular, medullary)
* Merkel Cell Carcinoma (skin)
* Nasopharyngeal Carcinoma
* Oral Cavity and Lip Cancer
* Laryngeal Cancer
* Anal Cancer
* Testicular Cancer (seminoma, non-seminoma)
* Adrenocortical Carcinoma

## Sarcomas (Connective Tissue Cancers)

* Osteosarcoma (bone)
* Ewing Sarcoma (bone, soft tissue)
* Chondrosarcoma (cartilage)
* Liposarcoma (fat)
* Leiomyosarcoma (smooth muscle)
* Rhabdomyosarcoma (skeletal muscle)
* Synovial Sarcoma
* Malignant Fibrous Histiocytoma
* Angiosarcoma (blood vessels)
* Kaposi Sarcoma (soft tissue)
* Fibrosarcoma
* Dermatofibrosarcoma Protuberans

## Hematologic Cancers (Blood and Immune System)

* Myelodysplastic Syndromes
* Myeloproliferative Neoplasms
* Cutaneous T-Cell Lymphoma (Mycosis Fungoides, Sézary Syndrome)
* Primary CNS Lymphoma

## Central Nervous System (CNS) Tumors

* Astrocytomas (including glioblastoma)
* Medulloblastoma
* Oligodendroglioma
* Ependymoma
* Craniopharyngioma
* Atypical Teratoid/Rhabdoid Tumor
* Germ Cell Tumors (CNS)
* Optic Nerve Glioma
* Meningioma

## Germ Cell Tumors

* Seminoma (testis)
* Dysgerminoma (ovary)
* Teratoma
* Yolk Sac Tumor
* Choriocarcinoma

## Blastomas (Embryonal Tumors, often in children)

* Neuroblastoma
* Retinoblastoma
* Nephroblastoma (Wilms Tumor)
* Hepatoblastoma
* Medulloblastoma

## Neuroendocrine Tumors

* Carcinoid Tumors (GI tract, lung)
* Pancreatic Neuroendocrine Tumors (insulinoma, gastrinoma, glucagonoma, VIPoma, somatostatinoma)
* Small Cell Lung Cancer (neuroendocrine)

## Other Specific Types and Syndromes

* Multiple Endocrine Neoplasia Syndromes (MEN)
* Langerhans Cell Histiocytosis
* Male Breast Cancer
* Metastatic Cancer (secondary tumors)
* Midline Tract Carcinoma with NUT Gene Changes

## 

## Carcinomas (Epithelial Cell Cancers)

| **Cancer Type** | **ICD-10-CM Code Range / Examples** |
| --- | --- |
| Adenocarcinoma (various organs) | Varies by site (e.g., C18.- colon, C25.- pancreas) |
| Basal Cell Carcinoma (skin) | C44.- (e.g., C44.01 Basal cell carcinoma of skin of lip, C44.111 Basal cell carcinoma of skin of right eyelid) [8](https://www.cancertherapyadvisor.com/home/tools/oncology-icd10-codes/) |
| Squamous Cell Carcinoma (skin, lung, head and neck) | C44.- for skin (e.g., C44.02 Squamous cell carcinoma of skin of lip) ; C32.- (larynx), C34.- (lung) |
| Transitional Cell Carcinoma (urothelial tract) | C65.- (renal pelvis), C66.- (ureter), C67.- (bladder) |
| Ductal Carcinoma In Situ (breast) | D05.1 (lobular carcinoma in situ), D05.0 (ductal carcinoma in situ) |
| Invasive Ductal Carcinoma (breast) | C50.- (breast cancer, site-specific) |
| Invasive Lobular Carcinoma (breast) | C50.- (breast cancer, site-specific) |
| Medullary Carcinoma (breast) | C50.- (breast cancer) with histology specified |
| Mucinous Carcinoma (breast, colon) | C50.- (breast), C18.- (colon), histology specified |
| Papillary Carcinoma (thyroid, breast) | C73 (thyroid), C50.- (breast) |
| Hepatocellular Carcinoma (liver) | C22.0 |
| Cholangiocarcinoma (bile duct) | C22.1 |
| Lung Cancer (Non-Small Cell, Small Cell) | C34.- (lung cancer), M8041/3 (small cell carcinoma, ICD-O histology code) |
| Pancreatic Adenocarcinoma | C25.- |
| Gastric (Stomach) Cancer | C16.- |
| Colorectal Cancer (colon, rectal) | C18.- (colon), C19-C20 (rectosigmoid, rectum) |
| Esophageal Cancer | C15.- |
| Cervical Cancer | C53.- |
| Endometrial (Uterine) Cancer | C54.- |
| Ovarian Cancer (epithelial types) | C56.- |
| Prostate Cancer | C61 |
| Bladder Cancer | C67.- |
| Renal (Kidney) Cell Carcinoma | C64.- |
| Thyroid Cancer (papillary, follicular, medullary) | C73 (thyroid) |
| Merkel Cell Carcinoma (skin) | C44.- (skin) with histology specified |
| Nasopharyngeal Carcinoma | C11.- |
| Oral Cavity and Lip Cancer | C00-C06 |
| Laryngeal Cancer | C32.- |
| Anal Cancer | C21.- |
| Testicular Cancer (seminoma, non-seminoma) | C62.- |
| Adrenocortical Carcinoma | C74.0 |

## Sarcomas (Connective Tissue Cancers)

| **Cancer Type** | **ICD-10-CM Code Range / Examples** |
| --- | --- |
| Osteosarcoma (bone) | C40.- (long bones), C41.- (other bones) |
| Ewing Sarcoma (bone, soft tissue) | C40.-, C49.- (soft tissue sarcomas) |
| Chondrosarcoma (cartilage) | C41.- |
| Liposarcoma (fat) | C49.- |
| Leiomyosarcoma (smooth muscle) | C49.- |
| Rhabdomyosarcoma (skeletal muscle) | C49.- |
| Synovial Sarcoma | C49.- |
| Malignant Fibrous Histiocytoma | C49.- |
| Angiosarcoma (blood vessels) | C49.- |
| Kaposi Sarcoma (soft tissue) | C46.- |
| Fibrosarcoma | C49.- |
| Dermatofibrosarcoma Protuberans | C49.- |

## Hematologic Cancers (Blood and Immune System)

| **Cancer Type** | **ICD-10-CM Code Range / Examples** |
| --- | --- |
| Acute Lymphoblastic Leukemia (ALL) | C91.0 |
| Acute Myeloid Leukemia (AML) | C92.0, C92.4, etc. |
| Chronic Lymphocytic Leukemia (CLL) | C91.1 |
| Chronic Myelogenous Leukemia (CML) | C92.1 |
| Hairy Cell Leukemia | C91.4 |
| Hodgkin Lymphoma | C81.- |
| Non-Hodgkin Lymphoma | C82.- to C85.- |
| Multiple Myeloma / Plasma Cell Neoplasms | C90.- |
| Myelodysplastic Syndromes | D46.- |
| Myeloproliferative Neoplasms | D47.1, D47.3 |
| Cutaneous T-Cell Lymphoma | C84.- |
| Primary CNS Lymphoma | C71.- (brain) with lymphoma histology |

## Central Nervous System (CNS) Tumors

| **Cancer Type** | **ICD-10-CM Code Range / Examples** |
| --- | --- |
| Astrocytomas (incl. glioblastoma) | C71.- (brain) |
| Medulloblastoma | C71.6 (cerebellum) |
| Oligodendroglioma | C71.- |
| Ependymoma | C71.- |
| Craniopharyngioma | D44.3 (benign neoplasm of pituitary gland) |
| Atypical Teratoid/Rhabdoid Tumor | C71.- |
| Germ Cell Tumors (CNS) | C71.- |
| Optic Nerve Glioma | C72.3 |
| Meningioma | D32.- (benign), C70.- (malignant meningeal tumors) |

## Germ Cell Tumors

| **Cancer Type** | **ICD-10-CM Code Range / Examples** |
| --- | --- |
| Seminoma (testis) | C62.0 |
| Dysgerminoma (ovary) | C56.9 |
| Teratoma | C62.- (testis), C56.- (ovary) |
| Yolk Sac Tumor | C62.-, C56.- |
| Choriocarcinoma | C58 (placenta), C62.- (testis) |

## Blastomas (Embryonal Tumors)

| **Cancer Type** | **ICD-10-CM Code Range / Examples** |
| --- | --- |
| Neuroblastoma | C74.9 (adrenal gland) |
| Retinoblastoma | C69.2 |
| Nephroblastoma (Wilms Tumor) | C64.9 (kidney) |
| Hepatoblastoma | C22.0 (liver) |
| Medulloblastoma | C71.6 (cerebellum) |

## Neuroendocrine Tumors

| **Cancer Type** | **ICD-10-CM Code Range / Examples** |
| --- | --- |
| Carcinoid Tumors (GI tract, lung) | C7A.- (malignant neuroendocrine tumors) |
| Pancreatic Neuroendocrine Tumors | C25.- with neuroendocrine histology |
| Small Cell Lung Cancer | C34.90 (lung, unspecified), M8041/3 (histology) |

## **CPT Codes f**or Carcinomas (Epithelial Cell Cancers)

## Skin Cancers (Basal Cell, Squamous Cell, Merkel Cell Carcinoma)

* Excision of malignant skin lesion:
  + 11640–11646 (size and location dependent)
* Mohs micrographic surgery:
  + 17311–17315
* Biopsy of skin lesion:
  + 11102 (shave biopsy), 11104 (punch biopsy), 11105 (incisional biopsy)

## Breast Carcinomas (Ductal, Lobular, Medullary, Mucinous, Papillary)

* Breast biopsy:
  + 19100 (percutaneous), 19101 (open)
* Lumpectomy (excision of breast tumor):
  + 19301 (partial mastectomy)
* Mastectomy:
  + 19303 (simple), 19307 (modified radical), 19305 (subcutaneous)
* Sentinel lymph node biopsy:
  + 38500, 38525
* Breast reconstruction:
  + 19340–19357

## Urothelial Tract (Transitional Cell Carcinoma)

* Cystoscopy with biopsy or fulguration:
  + 52000, 52204, 52214
* Transurethral resection of bladder tumor (TURBT):
  + 52234, 52235

## Lung Cancer (Non-Small Cell, Small Cell)

* Bronchoscopy with biopsy:
  + 31622–31623
* Thoracotomy with lung resection:
  + 32480–32482 (lobectomy, pneumonectomy)

## Gastrointestinal Cancers (Gastric, Colorectal, Esophageal)

* Endoscopic biopsy:
  + 43235 (esophagus), 45380 (colon)
* Esophagectomy:
  + 43117–43118
* Colectomy:
  + 44140–44147

## Gynecologic Cancers (Cervical, Endometrial, Ovarian)

* Colposcopy with biopsy:
  + 57452
* Hysterectomy:
  + 58150 (total abdominal), 58260 (laparoscopic)
* Oophorectomy:
  + 58940 (laparoscopic), 58943 (open)

## Prostate Cancer

* Prostate biopsy:
  + 55700
* Radical prostatectomy:
  + 55840

## Bladder Cancer

* Cystoscopy with biopsy or resection:
  + 52000, 52234

## Kidney Cancer (Renal Cell Carcinoma)

* Nephrectomy:
  + 50220 (radical), 50230 (partial)

## Thyroid Cancer (Papillary, Follicular, Medullary)

* Thyroid biopsy (fine needle aspiration):
  + 10022
* Thyroidectomy:
  + 60240 (total), 60252 (partial)

## Head and Neck Cancers (Nasopharyngeal, Oral Cavity, Laryngeal)

* Biopsy of lesion:
  + 42400 (oral cavity), 31505 (larynx)
* Resection of tumor:
  + 42420–42425 (oral cavity), 31360 (larynx)

## Anal Cancer

* Biopsy:
  + 46200
* Excision:
  + 46240

## Testicular Cancer

* Orchiectomy:
  + 54520

## Adrenocortical Carcinoma

* Adrenalectomy:
  + 60540 (laparoscopic), 60545 (open)

## CPT Codes for Sarcomas (Connective Tissue Cancers)

* Biopsy of soft tissue mass:
  + 20206 (open), 20220 (needle)
* Excision of soft tissue tumor:
  + 21930 (upper arm), 23065 (shoulder)
* Bone biopsy:
  + 20200 (needle), 20205 (open)
* Resection of bone tumor:
  + 27124 (femur), 27724 (tibia)

## CPT Codes for Hematologic Cancers (Leukemias, Lymphomas, Myeloma)

* Bone marrow biopsy and aspiration:
  + 38220, 38221
* Lymph node biopsy:
  + 38500 (superficial), 38525 (sentinel node)
* Chemotherapy administration:
  + 96401–96425 (various routes and settings)
* Stem cell transplantation:
  + 38240 (autologous), 38241 (allogeneic)

## CPT Codes for CNS Tumors

* Brain biopsy:
  + 61510 (stereotactic), 61519 (open)
* Craniotomy for tumor resection:
  + 61582–61585
* Lumbar puncture:
  + 62270 (diagnostic)

## CPT Codes for Germ Cell Tumors, Blastomas, Neuroendocrine Tumors

* Testicular biopsy:
  + 54500
* Nephroblastoma surgery:
  + 50740 (nephrectomy)
* Neuroblastoma biopsy/surgery:
  + 60505 (adrenalectomy)
* Carcinoid tumor biopsy/resection:
  + 43235 (endoscopic biopsy of GI tract)

### Acoustic Neuroma

**Definition and description**

An acoustic neuroma is a noncancerous tumor that develops on the main nerve leading from the inner ear to the brain. This nerve is called the vestibular nerve. Branches of the nerve directly affect balance and hearing. Pressure from an acoustic neuroma can cause hearing loss, ringing in the ear and trouble with balance. Another name for an acoustic neuroma is vestibular schwannoma.

An acoustic neuroma develops from the Schwann cells covering the vestibular nerve. A Schwann cell helps protect and support other nerve cells in the body. An acoustic neuroma is usually slow growing. Rarely, it may become large enough to press against the brain and affect vital functions.

Treatments for an acoustic neuroma include monitoring, radiation and surgical removal.

**Symptoms**

Symptoms of an acoustic neuroma often are easy to miss and may take years to develop. Symptoms may occur because of the tumor's effects on the hearing and balance nerves. The tumor also can put pressure on the facial nerve that directs facial muscles and the trigeminal nerve that affects feeling in the face. Blood vessels or other brain structures also can be affected by an acoustic neuroma.

As the tumor grows, it may be more likely to cause more noticeable or worse symptoms.

Common signs and symptoms of an acoustic neuroma include:

* Hearing loss, usually gradually over months to years. In rare cases, hearing loss can be sudden. Hearing loss usually occurs on one side or is worse on one side.
* Ringing in the affected ear, known as tinnitus.
* Loss of balance or not feeling steady.
* Dizziness.
* Facial numbness and, very rarely, weakness or loss of muscle movement.

Rarely, an acoustic neuroma may grow large enough to compress the brainstem and become life-threatening.

When to see your doctor

See a healthcare professional if you notice hearing loss in one ear, ringing in your ear or trouble with balance.

Early diagnosis of an acoustic neuroma may help keep the tumor from growing large enough to cause complications such as total hearing loss.

Causes

The cause of acoustic neuromas can sometimes be linked to a change to a gene on chromosome 22. Typically, this gene produces a tumor suppressor protein that helps regulate the growth of Schwann cells covering the nerves. Experts don't know what causes this change to the gene. Often there is no known cause. In some people, the gene change is related to a rare condition called NF2-related schwannomatosis, also known as NF2. The condition was previously known as neurofibromatosis type 2. People with NF2 usually have growth of tumors on the hearing and balance nerves on both sides of the head. These tumors are known as bilateral vestibular schwannomas.

Risk Factor

The only confirmed risk factor for acoustic neuromas is having a parent with the rare genetic condition NF2-related schwannomatosis, also known as NF2. However, only a small number of people with acoustic neuromas have NF2.

A hallmark characteristic of NF2 is noncancerous tumors on the balance nerves on both sides of the head. Tumors also may develop on other nerves.

NF2 is known as an autosomal dominant condition. This means that the gene related to the condition can be passed to a child by just one parent. Each child of an affected parent has a 50-50 chance of inheriting it.

Complications

An acoustic neuroma may cause permanent complications, including:

* Hearing loss.
* Facial numbness and weakness.
* Trouble with balance.
* Ringing in the ear.

Large tumors may press on the brain stem, occasionally preventing the flow of cerebrospinal fluid between the brain and spinal cord. Fluid can build up in your head, a condition known as hydrocephalus. This increases the pressure inside the skull.

**Diagnosis**

An acoustic neuroma often is hard to diagnose in the early stages because symptoms may be easy to miss and develop slowly over time. Common symptoms such as hearing loss also are associated with many other middle and inner ear issues.

After asking questions about your symptoms, a member of your healthcare team conducts an ear exam. You may need the following tests:

* **Hearing test, known as audiometry.** This test is conducted by a hearing specialist called an audiologist. During the test, sounds of various tones are directed to one ear at a time. You indicate each time you hear the sound. Each tone is repeated at fainter levels to find out when you can barely hear. The audiologist also may use words to test your hearing.
* **Imaging.** Magnetic resonance imaging (MRI) with contrast dye is usually used to diagnose an acoustic neuroma. This imaging test can detect tumors as small as 1 to 2 millimeters in diameter. If MRI is not available or you can't have an MRI scan, a CT scan may be done. However, CT scans may miss small tumors.

Treatment

Your acoustic neuroma treatment may vary, depending on:

* The size and growth rate of the acoustic neuroma.
* Your overall health.
* Your signs and symptoms.

There are three treatment approaches for acoustic neuroma: monitoring, surgery or radiation therapy.

Monitoring

You and your healthcare team may decide to monitor an acoustic neuroma if it's small and isn't growing or if it's growing slowly. This may be an option if the acoustic neuroma causes few or no symptoms. Monitoring also may be recommended if you're an older adult or if you're not a good candidate for more-aggressive treatment.

While being monitored, you'll need regular imaging and hearing tests, usually every 6 to 12 months. These tests can determine whether the tumor is growing and how quickly. If the scans show the tumor is growing or if the tumor causes worse symptoms, you may need to have surgery or radiation.

Surgery

You may need surgery to remove an acoustic neuroma, especially if the tumor is:

* Continuing to grow.
* Very large.
* Causing symptoms.

Your surgeon may use one of several techniques for removing an acoustic neuroma. The type of surgery your surgeon chooses depends on the size of the tumor, your hearing status and other factors.

The goal of surgery is to remove the tumor and preserve the facial nerve to prevent the paralysis of muscles in your face. Removing the entire tumor may not always be possible. For example, if the tumor is too close to important parts of the brain or the facial nerve, only part of the tumor may be removed.

Surgery for an acoustic neuroma is performed under general anesthesia. Surgery involves removing the tumor through the inner ear or through a window in your skull.

Sometimes removing the tumor may worsen symptoms if the hearing, balance or facial nerves are irritated or damaged during the operation. Hearing may be lost on the side where the surgery is performed. Balance is usually affected temporarily.

**Complications may include:**

* Leaking of the fluid that surrounds your brain and spinal cord, known as cerebrospinal fluid. Leaking may happen through the wound.
* Hearing loss.
* Facial weakness or numbness.
* Ringing in the ear.
* Trouble with balance.
* Persistent headache.
* Rarely, infection of the cerebrospinal fluid, known as meningitis.
* Very rarely, stroke or brain bleeding.

Radiation therapy

There are several types of radiation therapy used to treat an acoustic neuroma:

* **Stereotactic radiosurgery.** This type of radiation therapy is often used if the tumor is small — less than 2.5 centimeters in diameter. It also may be used if you are an older adult or you cannot have surgery for health reasons. This technique uses many tiny gamma rays to deliver a precisely targeted dose of radiation to a tumor. It treats the tumor without making an incision or damaging surrounding tissue.  
  The goal of stereotactic radiosurgery, such as Gamma Knife and CyberKnife, is to stop the growth of a tumor. The treatment also aims to preserve the facial nerve's function and possibly preserve hearing. It may take weeks, months or years before you notice the effects of radiosurgery. Your healthcare team monitors your progress with follow-up imaging studies and hearing tests.  
  Risks of radiosurgery include:
  + Hearing loss.
  + Ringing in the ear.
  + Facial weakness or numbness.
  + Trouble with balance.
  + Continued tumor growth.
* **Fractionated stereotactic radiotherapy.** Fractionated stereotactic radiotherapy, also called SRT, delivers a small dose of radiation to the tumor over several sessions. SRT is done to slow the growth of the tumor without damaging surrounding brain tissue.
* **Proton beam therapy.** This type of radiation therapy uses high-energy beams of positively charged particles called protons. The proton beams are delivered to the affected area in targeted doses to treat tumors. This type of therapy lowers radiation exposure to the surrounding area.

Supportive therapy

In addition to treatment to remove or stop the growth of the tumor, supportive therapies can help reduce your symptoms. The therapies help with dizziness, trouble with balance or other complications. For hearing loss, you can use cochlear implants or other treatments.

Treatment Options and Associated Side Effects

1. Monitoring ("Watch and Wait")

* Suitable for small tumors without symptoms or slow-growing tumors, especially in older patients or those with other health problems.
* Involves regular MRI scans and hearing tests.
* No drug-related side effects as no medication is used.

2. Surgery

* Surgical removal of the tumor is often highly effective.
* Risks and side effects include:
  + Hearing loss (especially if hearing is already compromised)
  + Facial nerve weakness or paralysis
  + Balance problems
  + Numbness or tingling in the face
  + Cerebrospinal fluid leaks or infection (rare)
* Surgery aims to preserve facial nerve function and remaining hearing as much as possible.

3. Radiation Therapy

* Includes stereotactic radiosurgery (e.g., Gamma Knife), fractionated stereotactic radiotherapy (SRT), and proton beam therapy.
* Goal is to stop or slow tumor growth, not to remove it.
* Side effects can include:
  + Hearing loss or worsening hearing
  + Ringing in the ear (tinnitus)
  + Facial weakness or numbness
  + Balance difficulties
  + Rarely, radiation-induced injury to surrounding brain tissue

**Diagnostic Considerations**

Differential diagnoses include the following:

* Meningiomas
* Facial neuromas or schwannomas
* Hemangiomas
* Vascular malformations
* Epidermoids
* Dermoids
* Cholesterol granulomas
* Lipomas
* Choroid plexus tumors
* Endolymphatic sac tumors
* Metastases

**Differential Diagnoses**

* Lipomas

## 

**Staging**

Koos staging system:

* Grade 1 - Tumor involvement includes only the internal auditory canal
* Grade 2 - The tumor extends into the cerebellopontine angle but does not contact the brain stem; maximum tumor diameter is 20 mm
* Grade 3 - The tumor fills the cerebellopontine angle without brain stem displacement
* Grade 4 - The brain stem is compressed by the tumor, and the cranial nerves are displaced

Inner ear schwannoma (IES) classification

A small subset of acoustic neuromas are intralabyrinthine, meaning that they originate from the bony labyrinth (cochlea or vestibule) rather than the internal auditory canal or cerebellopontine angle. While there are a variety of classification systems for these tumors, a multidisciplinary group met during the Ninth Quadrennial Conference on Vestibular Schwannoma and Other Cerebellopontine Angle Lesions, in Bergen, Norway to establish an updated classification system for such lesions.

* Intravestibular - Involving the vestibule +/- the semicircular canals (SCCs)
* Intracochlear - Involving the cochlea
* Intra Vestibulocochlear - Involving the cochlea AND vestibule +/- the SCCs
* Transfundal without modiolar involvement - Originating from the vestibule and extending into the internal auditory canal +/- the SCCs
* Transfundal with modiolar involvement - Originating from the cochlea and extending into the internal auditory canal

## 

**Epidemiology**

Frequency

Traditionally, the estimated incidence of vestibular schwannomas was 1 per 100,000 persons. However, with the increasing usage of MRI technology, there has been an increase in the number of incidentally found vestibular schwannomas. A meta-analysis by Marinelli et al identified six studies regarding national and international incidence rates of vestibular schwannomas, in Denmark, the Netherlands, Taiwan, and the United States. The incidence rate ranged from 3.0-5.2 per 100,000 person-years. Incidence was also found to increase with age, with one study identifying a rate of 20.6 per 100,000 person-years among patients over age 70 years.

**Outlook / Prognosis**

That depends on your condition, the type of surgery you have and any possible complications. Your provider will explain your treatment plan and what to expect, including:

* Treatment options if the tumor comes back
* Hearing devices that may help after surgery, like bone conduction implants or CROS (contralateral routing of signals) hearing aids

## 

**Procedures and Timelines**

1. Monitoring ("Watch and Wait")

* Recommended for small tumors with minimal symptoms or slow growth, especially in older patients or those with other health issues.
* Involves regular MRI scans and hearing tests every 6 to 12 months to track tumor growth.
* No immediate intervention; treatment initiated if tumor grows or symptoms worsen.

2. Surgical Removal

Goal: Remove tumor while preserving facial nerve function and, if possible, hearing.

Surgical Approaches:

* Translabyrinthine Approach:
  + Access through the inner ear; sacrifices hearing on the affected side.
  + Good visualization of facial nerves; suitable for large tumors.
* Retrosigmoid (Suboccipital) Approach:
  + Access through an opening at the base of the skull behind the ear.
  + Can be used for tumors of any size; hearing preservation possible in smaller tumors.
* Middle Fossa Approach:
  + Access through an incision above the ear.
  + Used primarily for small tumors (<2 cm) with good hearing; best chance of hearing preservation.

Timeline and Recovery:

* Hospital stay: Typically 3-4 days post-surgery.
* Return to driving: Around 3 weeks.
* Return to work: Usually 4-6 weeks, but can vary based on individual health and tumor size.
* Complete recovery: May take up to a year, with gradual improvement in balance and facial nerve function.
* Risks include hearing loss, facial weakness, balance problems, cerebrospinal fluid leak, and rare complications like infection or stroke.

3. Radiation Therapy (Stereotactic Radiosurgery)

* Most commonly performed as a single outpatient session using Gamma Knife or similar technologies.
* Delivers focused radiation to stop tumor growth rather than remove it.
* Suitable for small to medium tumors or patients who are poor surgical candidates.
* Minimal immediate recovery time; patients often resume normal activities quickly.
* Regular follow-up imaging is required to monitor tumor response.
* Side effects may include temporary headaches, fatigue, hearing loss, tinnitus, or facial numbness.

**Genomic Data**

Genomic Insights:

* NF2 Gene and Merlin Protein:  
  The NF2 gene encodes a tumor suppressor protein called *Merlin* (also known as schwannomin). Mutations in this gene lead to loss of Merlin function, resulting in uncontrolled Schwann cell proliferation and tumor formation on the vestibulocochlear nerve
* Sporadic vs. Genetic Cases
  + About 95% of acoustic neuromas are sporadic and unilateral, arising from spontaneous, non-hereditary mutations without a known genetic cause
  + The remaining ~5% are bilateral and hereditary, occurring in patients with Neurofibromatosis Type 2 (NF2), an autosomal dominant genetic disorder caused by germline mutations in the NF2 gene
* Neurofibromatosis Type 2 (NF2):
  + NF2 patients inherit one mutated copy of the NF2 gene and develop bilateral vestibular schwannomas, often in their teens or early adulthood
  + NF2 tumors may also occur on other cranial and spinal nerves.
  + About 50% of NF2 cases arise from new (de novo) mutations, with some cases showing mosaicism (mutation present in some but not all cells), influencing disease severity
* Mutation Types and Clinical Correlation:  
  Studies have identified multiple unique NF2 mutations, mostly truncating mutations that cause loss of function. Some milder missense mutations are linked to slower tumor growth and less severe clinical symptoms

**Questions & Answers Set**

1. What is likely causing my symptoms?

Your symptoms—such as hearing loss in one ear, tinnitus (ringing), dizziness, or balance problems—are likely caused by an acoustic neuroma, a benign tumor on the vestibulocochlear nerve that affects hearing and balance

2. Are there any other possible causes for my symptoms?

Yes. Similar symptoms can be caused by other middle or inner ear conditions, infections, or neurological disorders. Because these symptoms overlap with many other problems, further testing is needed to confirm acoustic neuroma

3. What kinds of tests do I need?

* Hearing test (audiometry): Measures hearing function, including pure tone average, speech reception, and discrimination. It helps detect asymmetry and degree of hearing loss
* Magnetic Resonance Imaging (MRI) with contrast: The gold standard for diagnosis; it detects tumors as small as 1-2 mm and shows their size and location clearly
* Additional tests: May include auditory brainstem response testing and balance assessments to evaluate nerve function

4. What treatment options are available?

There are three main approaches:

* Monitoring ("watch and wait"): For small, slow-growing tumors without significant symptoms
* Surgery: Tumor removal via approaches chosen based on tumor size and hearing status
* Radiation therapy (e.g., stereotactic radiosurgery): Non-invasive treatment to stop or slow tumor growth

5. Which one do you recommend for me?

The best treatment depends on:

* Tumor size and growth rate
* Your overall health and age
* Severity of symptoms
* Hearing status and preservation goals  
  Your doctor will discuss these factors with you to recommend monitoring, surgery, or radiation tailored to your situation

6. What is the likelihood of side effects from each treatment option?

* Monitoring: No treatment side effects, but risk of tumor growth and symptom progression.
* Surgery: Risks include hearing loss, facial nerve weakness or paralysis, balance problems, cerebrospinal fluid leak, and infection[2](https://www.mayoclinic.org/diseases-conditions/acoustic-neuroma/diagnosis-treatment/drc-20356132)[3](https://my.clevelandclinic.org/health/diseases/16400-acoustic-neuroma).
* Radiation therapy: Possible side effects include hearing loss, tinnitus, facial numbness or weakness, balance issues, and rarely radiation injury to brain tissue

7. What happens if I do nothing?

If untreated, the tumor may grow slowly and cause worsening hearing loss, balance problems, facial nerve dysfunction, and in rare cases, life-threatening brainstem compression. Regular monitoring is essential to detect changes early and intervene if needed

**Recent Guidelines**

The guidelines concerning hearing preservation in patients with sporadic vestibular schwannomas include the following:

* Patients whose baseline hearing meets the criteria for American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) class A or Gardner-Robertson hearing classification (GR) grade I and who are considering stereotactic radiosurgery utilizing modern dose planning should be counseled that there is a high probability (>75-100%) of hearing preservation at 2 years, a moderately high probability (>50-75%) of hearing preservation at 5 years, and a moderately low probability (>25-50%) of hearing preservation at 10 years
* Patients with AAO-HNS class A or GR grade I hearing at baseline who are considering microsurgical resection of small to medium-sized sporadic vestibular schwannomas should be counseled that there is a moderately high probability (>50-75%) of hearing preservation immediately following surgery, a moderately high probability (>50-75%) of hearing preservation at 2 years, a moderately high probability (>50-75%) of hearing preservation at 5 years, and a moderately low probability (>25-50%) of hearing preservation at 10 years
* Patients with AAO-HNS class A or GR grade I hearing at baseline should be counseled that, if they undergo management with conservative observation, there is a high probability (>75-100%) of hearing preservation at 2 years and a moderately high probability (>50-75%) of hearing preservation at 5 years; insufficient data were available to determine the probability of hearing preservation at 10 years for these patients

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1. <https://emedicine.medscape.com/article/882876-overview#a6>
2. <https://my.clevelandclinic.org/health/diseases/16400-acoustic-neuroma#outlook-prognosis>
3. <https://www.hopkinsmedicine.org/health/conditions-and-diseases/brain-tumor/vestibular-schwannoma>
4. [Acoustic neuroma - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/acoustic-neuroma/diagnosis-treatment/drc-20356132)

### 

### Adenocarcinoma

**Definition and description**

Carcinoma is the most common type of cancer overall. It begins in epithelial cells, which are found in various linings in the body, such as the skin, the mucous membranes coating the inside of the gastrointestinal tract, and the tissue layers surrounding the inside or outside of organs.

Adenocarcinoma is considered a carcinoma subtype. It develops in organs or other internal structures. The other main subtype of carcinoma is squamous cell carcinoma, which usually occurs in the skin.

Glands help the body function properly and keep organs moist. If glandular cells begin growing out of control, spurred by mutations that occur in the body’s DNA replication process, they may form tumors. Some tumors in glandular cells are not cancerous. They’re called adenomas. The malignant tumors are adenocarcinomas, which overtake healthy tissue inside an organ and may spread to other parts of the body.

Adenocarcinomas are generally first seen as a thickened, plaque-like white mucous membrane, according to the National Cancer Institute. They often spread easily through the soft tissue where they occur.

## Adenocarcinoma cancers

Many organs have glandular cells. Adenocarcinoma is often identified by its specific type, such as exocrine cancer in the pancreas, invasive ductal carcinoma in the breast or endometrial cancer in the uterus. Adenocarcinoma is most prevalent in the cancers below.

**Lung cancer:** Non-small cell lung cancer accounts for 80 percent of lung cancers, and adenocarcinoma of the lung is the most common type.

**ProstateAdenocarcinoma cancer:** Cancer that forms in the prostate gland is typically a prostate adenocarcinoma, which accounts for 99 percent of all prostate cancers.

**Pancreatic cancer:** Pancreatic adenocarcinomas form in the pancreas ducts and are the most common type of pancreatic cancer.

**Esophageal cancer:** Cancer that forms in the glandular cells of the esophagus is known as adenocarcinoma. Esophageal adenocarcinoma is the most common type of esophageal cancer.

**Colorectal cancer:** Cancer that develops in the intestinal gland cells that line the inside of the colon and/or rectum is an adenocarcinoma. It makes up 95 percent of colon and rectal cancers.

**Breast cancer:** The most common form of breast cancer, invasive ductal carcinoma, is an adenocarcinoma.

**Stomach cancer:** More than 90 percent of stomach cancer (gastric cancer) cases are gastric adenocarcinomas, either intestinal or diffuse.

It’s possible for adenocarcinoma to appear in the brain, usually from cancer that has metastasized from other areas of the body. Adenocarcinoma may also develop elsewhere in the body.

With so many different types of cancer under the heading of adenocarcinoma—and the metastases that are possible—there are many different risk factors and symptoms, depending on the specific disease.

## **Adenocarcinoma causes and risk factors**

The exact cause of adenocarcinoma is not known, but smoking is one risk factor that appears to apply to all adenocarcinomas.

Risk factors for adenocarcinoma vary depending on cancer type. It’s important to remember that risk factors don’t guarantee a cancer diagnosis; rather, they increase the odds of developing it. Some risk factors may be something patients are able to change, such as lifestyle factors.

### Lung adenocarcinoma

Lung adenocarcinoma is a type of non-small cell lung cancer (NSCLC) and the primary cause of death from cancer in the United States. As with other types of lung cancer, smoking is the biggest risk factor.

Other risk factors include:

* Exposure to secondhand smoke
* Air pollution or chemical irritants such as asbestos, radon, silica, heavy metals and diesel fumes
* Family history of lung adenocarcinoma

Some studies have found that taking beta carotene supplements and being exposed to arsenic in drinking water may increase lung cancer risk. Using talc or talcum powder and smoking marijuana or e-cigarettes are considered unproven risk factors.

### Prostate adenocarcinoma

The risk of prostate cancer increases after age 50, with the majority of cases found in men older than 65. Men of African ancestry are at increased risk.

A family history of the disease or inherited genetic mutations—such as the BRCA1 or BRCA2 genes—are associated risk factors, as is hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch syndrome.

### Pancreatic adenocarcinoma

The risk of pancreatic cancer rises with age, with most cases found in patients older than 65. Men develop pancreatic cancer more often than women, and race also plays a role, with African-Americans at a slightly higher risk.

Other risk factors include:

* Family history of the disease
* Inherited gene mutations causing chronic pancreatitis
* Inherited genetic syndromes

### Esophageal adenocarcinoma

Men are more likely than women to develop esophageal cancer. As with some other cancers, risk increases with age. The majority of cases are found in patients older than 55, according to the ACS.

Other risk factors include:

* Diet high in processed meat
* Frequent drinking of extremely hot liquids
* Tobacco use (chewing tobacco, cigarettes and cigars)
* Alcohol use
* Obesity
* Family history
* History of lung, mouth or throat cancer
* Human papillomavirus (HPV) infection
* Injury to the esophagus
* Gastroesophageal reflux disease (GERD)
* Barrett's esophagus, a condition in which chronic acid reflux damages the esophageal lining
* Achalasia, a condition in which the lower esophageal sphincter doesn’t function properly, causing irritation to the esophageal lining
* Tylosis, a genetic disease that may cause small growths on the esophagus
* Plummer-Vinson syndrome, a syndrome causing webs to form in the upper esophagus, possibly causing blockages, constriction or chronic irritation

### **Colorectal adenocarcinoma**

The greatest risk factors for colorectal cancer are age, gender and family history. Men are more likely than women to develop the disease.

Other risk factors include:

* Diet low in fiber and high in fat and processed meats
* Physical inactivity
* Obesity
* Alcohol use
* Tobacco use
* Inflammatory bowel disease (Crohn’s disease or ulcerative colitis)
* Colorectal polyps

### **Breast adenocarcinoma**

A family history of the disease as well as inherited genetic mutations (such as BRCA1 and BRCA2) raise the risk of breast cancer. Familial inheritance accounts for 5 percent to 10 percent of breast cancers.

Other risk factors include:

* Age (most cases are diagnosed in women age 55 and older)
* Early menstruation (especially before age 12)
* Menopause after age 55
* Dense breast tissue
* History of breast or ovarian cancer
* Prior radiation treatment to the chest area
* Alcohol use
* Obesity after menopause
* Physical inactivity

Women who have taken hormone replacement therapy or birth control, have never carried a full-term pregnancy or had their first child after age 30, or didn’t breastfeed, are at increased risk—as are women who took the drug diethylstilbestrol (DES), or whose mothers took the drug.

### **Gastric adenocarcinoma**

Men are more likely to develop stomach cancer, and risk increases with age. The majority of patients are diagnosed over the age of 60. stomach cancer is more often found among Hispanic-Americans, African Americans, Native Americans and Asian/Pacific Islanders than among whites in the United States.

Other factors include:

* Long-term Helicobacter pylori (H. pylori) infection (may lead to precancerous changes to the stomach lining)
* Excess weight or obesity
* Diet high in processed meat
* Alcohol and tobacco use
* Previous stomach surgeries
* Stomach polyps known as adenomas
* Menetrier disease (in which excess stomach lining growth causes low levels of stomach acid; exact link to stomach cancer isn’t known)
* Type A blood
* Common variable immune deficiency (CVID) (in which immune system fails to make enough antibodies)
* Previous Epstein-Barr virus infection

The following inherited conditions may also increase stomach cancer risk:

* Hereditary diffuse gastric cancer (HDGC)
* Hereditary non-polyposis colorectal cancer (HNPCC; Lynch syndrome)
* Familial adenomatous polyposis (FAP)
* Gastric adenoma and proximal polyposis of the stomach (GAPPS)
* Li-Fraumeni syndrome (LFS)
* Peutz-Jeghers syndrome (PJS)

## **Adenocarcinoma symptoms**

The symptoms of adenocarcinoma depend on the location of the cancer.

### Lung adenocarcinoma symptoms

Early symptoms of adenocarcinoma of the lung include:

* Fatigue
* Persistent cough
* Bloody sputum
* Shortness of breath
* Hoarseness
* Loss of appetite
* Weight loss
* Weakness
* Chest pain
* Wheezing
* Chronic or recurring infections (such as bronchitis and pneumonia)

### Prostate adenocarcinoma symptoms

Signs of adenocarcinoma of the prostate include:

* Frequent urination (especially at night)
* Difficulty fully emptying the bladder
* Weak urine flow
* Blood in the urine
* Erectile dysfunction
* Enlarged prostate that causes pain when sitting down
* Painful or burning when urinating

### **Pancreatic adenocarcinoma symptoms**

Symptoms of adenocarcinoma of the pancreas often don’t occur until the disease has progressed. When this occurs, a patient may experience:

* Jaundice (yellowing of the skin and eyes)
* Dark or brown urine
* Light or gray, greasy stools
* Itchiness
* Abdominal or back pain
* Weight loss
* Loss of appetite
* Nausea Vomiting
* Enlarged liver or gall
* bladder
* Blood clots
* Diabetes, but rarely

### **Esophageal adenocarcinoma symptoms**

Symptoms of adenocarcinoma of the esophagus include:

* Difficulty swallowing certain types of food
* Pain or choking with swallowing
* Chest pressure/burning
* Heartburn or indigestion
* Vomiting
* Coughing
* Hoarseness
* Pain behind breastbone or in throat
* Weight loss

### **Colorectal adenocarcinoma symptoms**

Symptoms of adenocarcinoma of the colon or rectum include:

* Changes to bowel habits, such as diarrhea, narrowed stool or constipation
* Persistent urge to have a bowel movement
* Rectal bleeding or bloody stool
* Abdominal pain or cramping
* Fatigue
* Weakness
* Weight loss

### **Breast adenocarcinoma symptoms**

Symptoms of adenocarcinoma of the breast include:

* Lump in the breast or under the armpit
* Thickening of the breast
* Breast swelling
* Irritation to the skin of the breast
* Dimpled breast skin
* Red or flaky skin around the nipple
* Nipple discharge
* Changes to the shape and/or size of the breast
* Breast pain

### **Gastric adenocarcinoma symptoms**

Symptoms of adenocarcinoma of the stomach include:

* Diminished appetite
* Weight loss
* Abdominal pain or discomfort
* Fullness after eating small amounts of food
* Heartburn or indigestion
* Nausea
* Vomiting (possibly with blood)
* Abdominal bloating or fluid retention
* Bloody stool
* Anemia (which may cause weakness and tiredness)
* Jaundice

## **Diagnosing adenocarcinoma**

Because adenocarcinoma may develop in so many different areas of the body, the type of diagnostic tests used also vary.

Breast cancer is frequently found in its early stages during mammogram screenings. Prostate cancers are often detected through a prostate-specific antigen (PSA) blood test or a digital rectal exam (DRE). A colonoscopy may be used for diagnosing colon cancer, while bronchoscopy may be used to detect adenocarcinoma of the lung.

In general, the types of tests that are performed may include:

**Biopsy**: This procedure is used to remove a sample of abnormal tissue from the body. A pathologist will then examine the tissue under a microscope to see whether cancer is present. A biopsy may also be used to determine whether a cancer originated at the site of the biopsy or if it’s metastatic, meaning it developed in another part of the body.

**CT scan**: A computed tomography scan is an imaging procedure that takes detailed, three-dimensional X-ray pictures of abnormal tissue in the body. CT scans may also be used to determine how adenocarcinoma is responding to treatment.

**MRI**: Magnetic resonance imaging uses radiofrequency waves to create detailed cross-sectional images of different parts of the body.

**Blood tests**: These lab tests are used to detect specific chemicals in the blood that may be related to different adenocarcinomas.

## **Adenocarcinoma grade and differentiation**

When a biopsy sample is sent to a laboratory for analysis, a pathologist examines the specimen under a microscope. Pathologists are doctors who are experts at diagnosing disease. One of the jobs of a cancer pathologist is to assess how the cancer cells appear microscopically. Cancer cells may look abnormal or similar to healthy cells.

Differentiation refers to the degree of similarity or difference between the cancer cells and healthy cells.

* Cancer cells that appear somewhat similar to healthy cells tend to be slow-growing and are considered “well differentiated.”
* Very abnormal-looking cancer cells are “poorly differentiated” and more likely to spread quickly.

Doctors sometimes assign a grade to a tumor based on this cell differentiation. Typically, adenocarcinoma tumors are given one of three grades:

**Low grade**, which means the cells are well differentiated adenocarcinoma

**Intermediate grade**, which means the cells are moderately differentiated adenocarcinoma

**High grade**, which means the cells are poorly differentiated adenocarcinoma

Determining a cancer’s grade is an essential part of the diagnostic process for some adenocarcinomas, including those that affect the breast, kidney and prostate. For these types of cancer, the differentiation of cells is often highly related to their growth speed, and it may help inform a patient’s prognosis and treatment. However, for other cancers, such as adenocarcinoma of the lung, differentiation is usually not an accurate method of predicting the outcome or likelihood that the cancer will spread.

## **Adenocarcinoma stages**

Following an adenocarcinoma diagnosis, the care team will stage the cancer, which is helpful when creating a treatment plan. The guidelines around determining the adenocarcinoma stages may differ depending on where the cancer is located, but the following guidance may help patients understand the general adenocarcinoma stages.

**Stage 0 adenocarcinoma:** The cancer remains where it started and hasn't grown into nearby tissue.

**Stage 1 adenocarcinoma:** The cancer is small and contained to local tissue, and has not spread to nearby lymph nodes or to other organs.

**Stage 2 adenocarcinoma:** The cancer cells have more deeply spread into nearby tissue and possibly into local lymph nodes, but not to distant organs.

**Stage 3 adenocarcinoma:** The tumor may be larger than in stage 2, or the cancer cells may be observed in deeper tissue or lymph nodes.

**Stage 4 adenocarcinoma:** The cancer has spread to other body areas further away from the original location. Adenocarcinoma stage 4 is also referred to as metastatic adenocarcinoma.

## **Adenocarcinoma treatment**

Treatment for adenocarcinoma also varies depending on where it grows in the body. Treatments may include:

**Surgery**: Often the first line of treatment for adenocarcinoma, surgery is used to remove the cancerous glandular tissue and some surrounding tissue. If possible, minimally invasive surgical procedures may be used to help reduce healing time and the risk of post-surgical infection.

**Chemotherapy**: Chemotherapy uses drugs to kill cancer cells. Chemo drugs may be used throughout the body or in a specific area.

**Radiation therapy**: Often used in combination with surgery and/or chemotherapy, advanced radiation therapies use image guidance before and during treatment to target adenocarcinoma tumors and spare healthy tissues and surrounding organs.

**Targeted therapy**: Unlike chemotherapy, which kills healthy and cancerous cells, this treatment targets cancer cells directly. The therapy is designed to attack genetic features that regulate cells’ growth and division.

**Immunotherapy**: Rather than attack cancer cells directly, immunotherapy alerts the body’s immune system to the presence of the abnormal cells. That, in turn, triggers the body’s own immune response to attack the cancer.

## 

## **Adenocarcinoma survival rates**

Adenocarcinoma describes the type of cells in which the cancer begins (epithelial cells), not where in the body the cancer forms. As a result, the survival rate of adenocarcinoma is highly dependent on the patient’s circumstances, including the cancer’s location and stage, and whether or not other illnesses are present.

Usually, doctors use a five-year relative survival rate to communicate estimated outcomes to patients. A five-year relative survival rate shows the likelihood that a person with a specific type and stage of cancer may live for at least five years after the diagnosis, compared with people who don't have cancer. Doctors can sometimes provide three survival rates for each cancer type:

* One for those with localized disease (the cancer has not spread beyond its original location)
* A second for regional cases (the cancer has spread to areas near the original cancer location)
* A third for distant cancers (the cancer has spread to distant body parts)

Data from past patients is used to predict these average relative survival rates. They’re usually calculated by the cancer’s location and stage, but not by specific subtype, such as adenocarcinoma.

**Adenocarcinoma of the lung and bronchus:** The five-year relative survival rate of lung adenocarcinoma is 73.3 percent for localized cases, 46.4 percent for regional cases and 11 percent for distant cases. The overall five-year relative survival rate for adenocarcinoma of the lung and bronchus is 32.2 percent

**Adenocarcinoma of the esophagus:** The five-year relative survival rate for esophageal adenocarcinoma is 53.8 percent for localized cases, 28.6 percent for regional cases and 5.3 percent for distant cases. The overall five-year relative survival rate for adenocarcinoma of the esophagus is 22.9 percent

It’s important to recognize that these numbers are just estimates, based on averages rather than individuals. The patient's care team will be able to provide him or her with a more specific prognosis based on the type, stage and location of the cancer.

## **Metastatic adenocarcinoma (stage 4)**

### What is metastatic adenocarcinoma?

Adenocarcinoma that spreads to another part of the body is considered metastatic adenocarcinoma, which is also called stage 4 adenocarcinoma. When cancer spreads to another part of the body, it’s still named for the location of origin—so breast cancer that’s spread to the lung is still called breast cancer, or metastatic breast cancer of the lung, not lung cancer.

Cancer cells sometimes spread when they break off from the original tumor. They may travel through the bloodstream or lymph system to other parts of the body. Most of these cells die along the way, but some survive and find areas to grow. In the case of lung adenocarcinoma, cancer cells may also spread through airways in the lungs. Researchers are still learning about this type of spread, called aerogenous metastasis.

### Where do metastatic adenocarcinomas spread?

Since cancer often spreads through the bloodstream or lymph system, cancer cells are more likely to spread to the organ or set of lymph nodes “downstream” from where the primary cancer started. Breast cancer, for example, tends to spread to underarm lymph nodes. Metastatic adenocarcinomas most commonly spread to the bones, lungs, liver and/or lymph nodes, but they also may spread to other areas of the body.

In addition to nearby lymph nodes, certain types of adenocarcinomas are more likely to spread to these areas:

* Lung cancer: Brain, bones and adrenal glands
* Prostate cancer: Bones and liver
* Pancreatic cancer: Abdomen and liver
* Esophageal cancer: Brain, lungs, bones, liver and adrenal glands
* Colorectal cancer: Liver, brain, lungs and the peritoneum (the lining of the abdomen and some organs inside it)
* Breast cancer: Bones, liver, lungs and brain
* Stomach cancer: Liver and the peritoneum

### What causes metastatic adenocarcinoma?

Adenocarcinomas may be more likely to spread if the cancer cells are high-grade (also called poorly differentiated), which means they look different from normal cells under a microscope. High-grade cancers are aggressive and more likely to grow and become metastatic than low-grade cancers.

## **Epidemiology of Adenocarcinoma**

## Incidence and Prevalence

Adenocarcinomas constitute a significant proportion of common cancers worldwide. For example:

Lung adenocarcinoma is now the most common subtype of lung cancer, surpassing squamous cell carcinoma, driven by changes in smoking patterns and increased exposure to air pollution.

Colorectal adenocarcinoma is the predominant histologic type of colorectal cancer, one of the most common cancers globally.

Breast adenocarcinoma (invasive ductal carcinoma) is the most frequent breast cancer subtype.

Globally, cancer incidence is rising, with over 20 million new cancer cases estimated in 2022 and projected to increase to over 35 million by 2050, reflecting population growth, aging, and risk factor exposure (e.g., tobacco, obesity, pollution). Adenocarcinomas contribute substantially to this burden.

## 2. Risk Factors

Tobacco smoking and air pollution are major risk factors for lung adenocarcinoma.

Dietary patterns, obesity, and genetic predisposition influence colorectal adenocarcinoma risk.

Hormonal and reproductive factors, along with genetic mutations, affect breast adenocarcinoma risk.

Chronic inflammation and gastroesophageal reflux disease are linked to esophageal adenocarcinoma.

## 3. Demographics

Adenocarcinomas occur across all age groups but are more common in older adults due to cumulative exposures and genetic changes.

Incidence rates vary by sex and ethnicity; for example, lung adenocarcinoma incidence in women has surpassed men under age 65 in some populations.

Disparities exist globally and within countries, with higher mortality in underserved populations due to limited access to prevention and treatment.

## 4. Mortality

Adenocarcinomas of the lung, pancreas, and colon are among the leading causes of cancer death worldwide.

In the US, cancer mortality has been declining overall due to improved prevention and treatment, but disparities persist.

## 5. Trends

Lung adenocarcinoma rates have increased relative to other lung cancer types, linked to changes in smoking habits and environmental exposures.

Rising obesity and aging populations contribute to increased adenocarcinoma incidence in several organs.

#### 

#### **Side effects of adenocarcinoma surgery**

Some of the general side effects after adenocarcinoma surgery include:

* Loss of appetite.
* Nausea or vomiting.
* Pain or discomfort.
* Tiredness.

Be sure to tell your healthcare provider if you experience any side effects. They can help you find ways to ease your symptoms and make you more comfortable.

## **Outlook / Prognosis**

Adenocarcinoma outlook varies depending on the type, location and size of the tumor. Cancers that are hard to diagnose in the early stages are more likely to be fatal compared to cancers that are detectable early on.

Treatment can successfully manage adenocarcinoma in many cases. Survival rates vary depending on the type of cancer, its location and stage.

## **Prevention**

Even though you can’t prevent adenocarcinoma altogether, there are some things you can do to lower your risk:

* Avoid tobacco products.
* Increase physical activity.
* Eat a well-balanced diet.
* Maintain a weight that’s healthy for you.
* Visit your healthcare provider regularly.

## **Living With**

Going through adenocarcinoma treatment can leave you feeling helpless and frustrated. One way to regain a sense of control is to practice self-care. Here are some suggestions:

* Get lots of rest.
* Eat a well-balanced, nourishing diet.
* Take walks outside.
* Schedule a massage.
* Find time for activities that fulfill you.
* Practice mindfulness or meditation.

If you want to exercise, be sure that you talk to your healthcare provider before incorporating anything new into your routine. This will ensure that you stay as healthy as possible during treatment.

### **When should I see my healthcare provider?**

You should visit your healthcare provider if symptoms last longer than two weeks. If symptoms interfere with your daily life, schedule an appointment immediately.

**Question and answer set**

## What type of adenocarcinoma do I have?

Your doctor will determine the specific type based on where the cancer started (e.g., lung, colorectal, breast, pancreatic). Adenocarcinomas arise from glandular cells in different organs, so knowing the origin is key to treatment and prognosis.

## 2. Where is the cancer located?

The cancer location is identified through imaging and biopsy. Common sites include lungs, colon, breast, pancreas, prostate, and esophagus. Your doctor will explain the exact location based on your diagnostic tests.

## 3. Has it spread to other parts of my body?

Whether the cancer has spread (metastasized) depends on the stage at diagnosis. Your doctor uses scans and tests to check for spread to lymph nodes or distant organs. Early-stage adenocarcinomas are usually localized, while advanced stages may involve metastasis.

## 4. What are my treatment options?

Treatment depends on cancer type, location, stage, and your overall health. Options include:

* Surgery to remove the tumor
* Chemotherapy to kill cancer cells
* Radiation therapy
* Targeted therapies or immunotherapy for some advanced cases  
  Your oncologist will tailor a treatment plan specific to your situation.

## 5. How long will my treatment last?

Chemotherapy courses typically last 3 to 6 months, sometimes longer depending on cancer type and response. Multimodality treatment (combining surgery, chemo, radiation) can extend total treatment time to several months (e.g., 6–26 weeks or more).

## 6. What are the possible risks and side effects?

Common chemotherapy side effects include fatigue, nausea, hair loss, low blood counts, and increased infection risk. Radiation and surgery have their own risks such as localized pain or tissue damage. Side effects often improve after treatment ends but some can persist longer.

## 7. Can I work during treatment?

Many patients continue working during treatment, especially if side effects are mild. However, fatigue and other symptoms may require adjustments. Your healthcare team can help you plan and manage work during therapy.

## 8. What’s the goal of my treatment?

Goals vary:

* Curative: To eliminate cancer completely, especially in early stages
* Control: To shrink tumors and slow progression in advanced cases
* Palliative: To relieve symptoms and improve quality of life if cure isn’t possible

## 

## **What are common side effects of chemo?**

Side effects of chemo can be very different depending on the type you are getting. Here are some of the more common side effects caused by chemo:

* Fatigue
* Hair loss
* Thrombocytopenia (low platelet count)
* Neutropenia (low white blood counts)
* Increased risk of infection
* Anemia (low red blood cell counts)
* Nausea and vomiting
* Appetite changes
* Constipation
* Diarrhea
* Mouth sores
* Peripheral neuropathy or other nerve problems
* Skin and nail changes such as rash, dry skin and color change
* Bowel or bladder incontinence
* Weight changes
* Chemo brain, which can affect concentration and focus
* Anxiety
* Depression
* Changes in libido and sexual function
* Fertility problems

## **Chemo drug interactions and side effects**

When looking at how best to combine types of chemo, doctors must look at interactions between chemo drugs and other medicines the person is taking, including over-the-counter medicines, vitamins, and supplements. These interactions may make side effects worse and affect how well chemo works.

It’s important that you tell your doctor about all medicines, including over-the-counter medicines, vitamins, and herbal or dietary supplements you are taking—even if you only take them “as needed.”

For instance, platelets help blood clot and prevent bleeding. Many types of chemo lower the number of platelets for a time. Taking aspirin or other related medicines can also weaken blood platelets. This isn’t a problem for healthy people with normal platelet counts, but if a person has low platelet counts from chemo, this combination might put them at risk of a serious bleeding problem.

Your doctor can talk with you about the safety of using other medicines, vitamins, and supplements while you are being treated for cancer.

## **How vitamins affect chemo**

Many people want to take an active role in improving their overall health. They want to help their body’s natural defenses fight the cancer and speed up their recovery from chemo. Most people think of vitamins as a safe way to improve health, so it’s not surprising that many people with cancer take high doses of one or more vitamins. But some vitamins might make chemo less effective.

More research is needed, but until more is known about the effects of vitamins on chemo, keep these points in mind:

* Unless your doctor tells you to take certain vitamins, it’s best not to take any.
* Always check with your doctor first before starting to take a vitamin of any kind, even a simple multivitamin.
* Ask your doctors if and when it might be OK to start taking vitamins after treatment.
* If you’re concerned about nutrition, you can usually get plenty of vitamins by eating a well-balanced diet.

**Common Eating-Related Side Effects**

## Loss of appetite and unintentional weight loss

## Nausea and vomiting

## Diarrhea or constipation

## Dry mouth and thick saliva

## Mouth sores or painful swallowing

## Taste changes (food may taste bitter, metallic, or bland)

## Feeling full quickly (early satiety)

## Fatigue, which can reduce motivation to eat

## Difficulty chewing or swallowing (especially after surgery or radiation to head/neck areas)

## **Practical Tips to Manage Side Effects**

## 1. Loss of Appetite & Weight Loss

## Eat small, frequent meals and snacks throughout the day.

## Choose nutrient-dense, high-calorie foods (e.g., nuts, avocados, smoothies).

## Use oral nutrition supplements if recommended by your healthcare team.

## Eat your favorite foods when you feel hungry, even if they are not “perfectly healthy.”

## Avoid strong food odors that may trigger nausea.

## 2. Nausea and Vomiting

## Eat bland, easy-to-digest foods (e.g., crackers, toast, rice).

## Avoid greasy, spicy, or fried foods.

## Sip fluids slowly and frequently to stay hydrated.

## Take anti-nausea medications as prescribed.

## Try ginger or peppermint tea, which may help reduce nausea.

## 3. Diarrhea and Constipation

## For diarrhea: Eat low-fiber, binding foods like bananas, rice, applesauce, and toast (BRAT diet). Stay hydrated.

## For constipation: Increase fiber intake gradually (fruits, vegetables, whole grains), drink plenty of fluids, and stay as active as possible. Your doctor may recommend stool softeners or laxatives.

## 4. Dry Mouth and Mouth Sores

## Drink plenty of fluids, especially water.

## Use saliva substitutes or oral moisturizers.

## Avoid acidic, spicy, or rough-textured foods that irritate the mouth.

## Eat soft, cool, or pureed foods.

## Maintain good oral hygiene with gentle brushing.

## 5. Taste Changes

## Experiment with herbs, spices, or marinades to improve flavor.

## Try cold or room-temperature foods if hot foods taste unpleasant.

## Use plastic utensils if metal tastes are bothersome.

## Rinse your mouth before and after eating.

## 6. Feeling Full Quickly (Early Satiety)

## Eat smaller portions more frequently.

## Choose nutrient-rich liquids like smoothies or meal replacement shakes.

## Avoid drinking large amounts of fluids before or during meals.

## 7. Fatigue

## Plan meals and snacks for times when you have more energy.

## Ask family or friends for help with shopping and meal preparation.

## Consider easy-to-prepare or ready-to-eat nutritious foods.

## Additional Recommendations

## Food Safety: Chemotherapy can lower immunity, increasing infection risk. Avoid raw or undercooked foods, unpasteurized dairy, and foods that may harbor bacteria.

## Hydration: Drink fluids regularly to prevent dehydration, especially if experiencing diarrhea or vomiting.

## Professional Support: Consult a dietitian or nutritionist specialized in cancer care for personalized advice.

## Medication Management: Use prescribed medications for symptom control (antiemetics, pain relief, stool softeners) as directed.

## 

## 

## **Chemotherapy Drugs**

Chemotherapy drugs kill rapidly dividing cancer cells but can also affect healthy fast-growing cells, causing side effects.

## Common Chemotherapy Agents for Adenocarcinoma (depending on site):

* Platinum-based drugs: Cisplatin, Carboplatin
* Taxanes: Paclitaxel, Docetaxel
* Antimetabolites: 5-Fluorouracil (5-FU), Capecitabine, Gemcitabine
* Topoisomerase inhibitors: Irinotecan, Topotecan
* Anthracyclines: Doxorubicin (less common in adenocarcinomas)

(Exact drugs depend on adenocarcinoma location, e.g., lung, colon, pancreas.)

**Procedures and timeline**

## Diagnosis and Staging

* Initial diagnosis involves biopsy and imaging (CT, MRI, PET scans) to determine tumor type, size, and spread.
* Staging (0 to IV) assesses how far the cancer has grown locally and if it has spread to lymph nodes or distant organs.

## 2. Treatment Procedures

## Surgery

* Goal: Remove the tumor and some surrounding healthy tissue.
* When: Often first-line for early-stage adenocarcinoma (Stages 0, I, II).
* Additional: Lymph node removal may be performed to check for spread.
* Recovery: Hospital stay varies by organ and surgery type (e.g., lung surgery may require 5–7 days hospital stay).
* Timeline: Surgery is usually a one-time procedure followed by recovery over weeks to months.

## Chemotherapy

* Goal: Kill cancer cells systemically or shrink tumors before surgery (neoadjuvant) or after surgery (adjuvant).
* When: Used in stages II–IV or when surgery is not feasible.
* Duration: Typically cycles over 3–6 months, depending on regimen and response.

## Radiation Therapy

* Goal: Destroy cancer cells locally, often used when surgery isn’t possible or as adjuvant therapy.
* Duration: Usually daily treatments over 3–7 weeks.

## Targeted Therapy and Immunotherapy

* Goal: Target specific genetic mutations or boost immune response.
* When: Advanced or metastatic adenocarcinoma, or when standard treatments fail.
* Duration: Ongoing until disease progression or unacceptable side effects.

## **Adenocarcinoma Differential Diagnosis**

### **Adenocarcinoma of the Lung**

The differential diagnosis of lung adenocarcinoma should include the following

* Chest infections, including tuberculosis and bacterial and [viral pneumonia](https://www.pulmonologyadvisor.com/ddi/viral-pneumonia/);
* Metastatic cancer from another primary location, such as prostate, breast, or urinary bladder cancer;
* Squamous cell carcinoma of the lung,
* Small cell carcinoma of the lung; and
* Malignant mesothelioma.

### **Adenocarcinoma of the Breast**

The differential diagnosis of breast adenocarcinoma should include the following

* Cysts;
* Fibroadenoma;
* Mammary duct ectasia;
* Intraductal papilloma;
* Metastatic disease from another primary location;
* Hyperplasia of the mammary glands; or
* Breast tuberculosis.

### **Adenocarcinoma of the Colon/Rectum**

The differential diagnosis of colorectal adenocarcinoma should include the following

* Irritable bowel syndrome;
* Inflammatory bowel disease, including Crohn’s disease and ulcerative colitis;
* Hemorrhoids; and
* Diverticular disease.

### **Adenocarcinoma of the Prostate**

The differential diagnosis of prostate adenocarcinoma should include the following

* Benign prostatic hyperplasia;
* Cysts;
* Acinar adenocarcinoma;
* Chronic prostatitis;
* Amyloidosis;
* Abscesses;
* Granulomatous prostatitis containing tuberculosis;
* Hemorrhage;
* Exophytic benign prostatic hyperplasia;
* Fibrosis;
* Atrophy; or
* Calcifications.

### **Adenocarcinoma of the Pancreas**

The differential diagnosis of pancreatic adenocarcinoma should include the following

* Autoimmune pancreatitis;
* Focal chronic pancreatitis; or
* Pancreatic endocrine tumors.

**Doctor-patient conversation about adenocarcinoma**

Doctor:  
“Hello, I have reviewed your test results, and you have been diagnosed with adenocarcinoma, which is a type of cancer that begins in glandular cells. This cancer can occur in various organs, so I want to explain what this means for you specifically.”

Patient:  
“What exactly is adenocarcinoma? How is it different from other cancers?”

Doctor:  
“Adenocarcinoma starts in cells that produce mucus or other fluids, and it can behave differently depending on where it develops. For example, lung adenocarcinoma and colorectal adenocarcinoma are both adenocarcinomas but have different treatments and outlooks. Understanding the exact location and stage of your cancer helps us tailor the best treatment plan.”

Patient:  
“Has the cancer spread beyond where it started?”

Doctor:  
“We have done imaging and scans, and based on those, your cancer is [localized / has spread to nearby lymph nodes / has distant metastases]. This information is important because it influences the treatment options and goals.”

Patient:  
“What treatment options do I have?”

Doctor:  
“Treatment depends on the cancer’s location and stage. Options often include surgery to remove the tumor, chemotherapy to kill cancer cells, radiation therapy, and sometimes targeted therapies or immunotherapy. We will choose the approach that offers the best chance for control or cure while considering your overall health.”

Patient:  
“How long will the treatment last? What side effects should I expect?”

Doctor:  
“Treatment duration varies but typically lasts several months. Chemotherapy side effects can include fatigue, nausea, and hair loss, but we have ways to manage these. Surgery recovery depends on the procedure. We will support you throughout and monitor for any side effects.”

Patient:  
“Will I be able to work during treatment?”

Doctor:  
“Many patients continue working during treatment, depending on how they feel and the intensity of therapy. We can discuss ways to balance treatment and daily activities.”

Patient:  
“What is the goal of my treatment?”

Doctor:  
“Our goal is to either cure the cancer or control it to improve your quality of life. We will regularly assess how well the treatment is working and adjust as needed.”

Patient:  
“Thank you for explaining. What should I do next?”

Doctor:  
“I will provide you with written information and reliable websites to learn more. Also, please write down any questions you have for our next visit. You can bring a family member or friend to help you remember the information.”

REFERENCES

<https://www.cancertherapyadvisor.com/ddi/adenocarcinoma/>

<https://www.cancer.org/cancer/managing-cancer/treatment-types/chemotherapy/chemotherapy-side-effects.html>

<https://my.clevelandclinic.org/health/diseases/21652-adenocarcinoma-cancers#overview>

[Adenocarcinoma: Cancer Types, Stages & Survival Rate](https://www.cancercenter.com/adenocarcinoma)

<https://www.cancer.org/content/dam/cancer-org/cancer-control/en/booklets-flyers/nutrition-for-the-patient-with-cancer-during-treatment.pdf>

**BASAL CELL CARCINOMA**

**DEFINITION AND DESCRIPTION**

Basal cell carcinoma is a type of skin cancer. Basal cell carcinoma begins in the basal cells — a type of cell within the skin that produces new skin cells as old ones die off.

Basal cell carcinoma often appears as a slightly transparent bump on the skin, though it can take other forms. Basal cell carcinoma occurs most often on areas of the skin that are exposed to the sun, such as your head and neck.

Most basal cell carcinomas are thought to be caused by long-term exposure to ultraviolet (UV) radiation from sunlight. Avoiding the sun and using sunscreen may help protect against basal cell carcinoma.

## 

## **Causes**

Basal cell carcinoma occurs when one of the skin's basal cells develops a mutation in its DNA.

Basal cells are found at the bottom of the epidermis — the outermost layer of skin. Basal cells produce new skin cells. As new skin cells are produced, they push older cells toward the skin's surface, where the old cells die and are sloughed off.

The process of creating new skin cells is controlled by a basal cell's DNA. The DNA contains the instructions that tell a cell what to do. The mutation tells the basal cell to multiply rapidly and continue growing when it would normally die. Eventually the accumulating abnormal cells may form a cancerous tumor — the lesion that appears on the skin.

### **Ultraviolet light and other causes**

Much of the damage to DNA in basal cells is thought to result from ultraviolet (UV) radiation found in sunlight and in commercial tanning lamps and tanning beds. But sun exposure doesn't explain skin cancers that develop on skin not ordinarily exposed to sunlight. Other factors can contribute to the risk and development of basal cell carcinoma, and the exact cause may in some cases not be clear.

## 

## **Risk factors**

Factors that increase your risk of basal cell carcinoma include:

* **Chronic sun exposure.** A lot of time spent in the sun — or in commercial tanning beds — increases the risk of basal cell carcinoma. The threat is greater if you live in a sunny or high-altitude location, both of which expose you to more ultraviolet (UV) radiation. Severe sunburns also increase your risk.
* **Radiation therapy.** Radiation therapy to treat acne or other skin conditions may increase the risk of basal cell carcinoma at previous treatment sites on the skin.
* **Fair skin.** The risk of basal cell carcinoma is higher among people who freckle or burn easily or who have very light skin, red or blond hair, or light-colored eyes.
* **Increasing age.** Because basal cell carcinoma often takes decades to develop, the majority of basal cell carcinomas occur in older adults. But it can also affect younger adults and is becoming more common in people in their 20s and 30s.
* **A personal or family history of skin cancer.** If you've had basal cell carcinoma one or more times, you have a good chance of developing it again. If you have a family history of skin cancer, you may have an increased risk of developing basal cell carcinoma.
* **Immune-suppressing drugs.** Taking medications that suppress your immune system, such as anti-rejection drugs used after transplant surgery, significantly increases your risk of skin cancer.
* **Exposure to arsenic.** Arsenic, a toxic metal that's found widely in the environment, increases the risk of basal cell carcinoma and other cancers. Everyone has some arsenic exposure because it occurs naturally. But some people may have higher exposure if they drink contaminated well water or have a job that involves producing or using arsenic.
* **Inherited syndromes that cause skin cancer.** Certain rare genetic diseases can increase the risk of basal cell carcinoma, including nevoid basal cell carcinoma syndrome (Gorlin-Goltz syndrome) and xeroderma pigmentosum.

## 

## **Symptoms**

Basal cell carcinoma usually develops on sun-exposed parts of your body, especially your head and neck. Less often, basal cell carcinoma can develop on parts of your body usually protected from the sun, such as the genitals.

Basal cell carcinoma appears as a change in the skin, such as a growth or a sore that won't heal. These changes in the skin (lesions) usually have one of the following characteristics:

* **A shiny, skin-colored bump** that's translucent, meaning you can see a bit through the surface. The bump can look pearly white or pink on white skin. On brown and Black skin, the bump often looks brown or glossy black. Tiny blood vessels might be visible, though they may be difficult to see on brown and Black skin. The bump may bleed and scab over.
* **A brown, black or blue lesion** — or a lesion with dark spots — with a slightly raised, translucent border.
* **A flat, scaly patch** with a raised edge. Over time, these patches can grow quite large.
* **A white, waxy, scar-like lesion** without a clearly defined border.

## 

## **Diagnosis**

In order to assess any growths or changes in your skin, your doctor or a specialist in skin conditions (dermatologist) will conduct a medical history and exam.

### **History and general exam**

Your doctor will conduct a general physical exam and ask you questions about your medical history, changes in your skin, or any other signs or symptoms you've experienced.

Questions may include:

* When did you first notice this skin growth or lesion?
* Has it changed since you first noticed it?
* Is the growth or lesion painful?
* Do you have any other growths or lesions that concern you?
* Have you had a previous skin cancer?
* Has anyone in your family had skin cancer? What kind?
* Do you take precautions to stay safe in the sun, such as avoiding midday sun and using sunscreen?
* Do you examine your own skin on a regular basis?

### **Skin exam**

Your doctor will examine not only the suspicious area on your skin but also the rest of your body for other lesions.

### **Skin sample for testing**

Your doctor may do a skin biopsy, which involves removing a small sample of a lesion for testing in a laboratory. This will reveal whether you have skin cancer and, if so, what type of skin cancer. The type of skin biopsy you undergo will depend on the type and size of the lesion.

## 

## **Treatment**

The goal of treatment for basal cell carcinoma is to remove the cancer completely. Which treatment is best for you depends on the type, location and size of your cancer, as well as your preferences and ability to do follow-up visits. Treatment selection can also depend on whether this is a first-time or a recurring basal cell carcinoma.

### **Surgery**

Basal cell carcinoma is most often treated with surgery to remove all of the cancer and some of the healthy tissue around it.

Options might include:

* **Surgical excision.** In this procedure, your doctor cuts out the cancerous lesion and a surrounding margin of healthy skin. The margin is examined under a microscope to be sure there are no cancer cells.  
  Excision might be recommended for basal cell carcinomas that are less likely to recur, such as those that form on the chest, back, hands and feet.
* **Mohs surgery.** During Mohs surgery, your doctor removes the cancer layer by layer, examining each layer under the microscope until no abnormal cells remain. This allows the surgeon to be certain the entire growth is removed and avoid taking an excessive amount of surrounding healthy skin.  
  Mohs surgery might be recommended if your basal cell carcinoma has a higher risk of recurring, such as if it's larger, extends deeper in the skin or is located on your face.

### **Other treatments**

Sometimes other treatments might be recommended in certain situations, such as if you're unable to undergo surgery or if you don't want to have surgery.

Other treatments include:

* **Curettage and electrodessication (C and E).** C and E treatment involves removing the surface of the skin cancer with a scraping instrument (curet) and then searing the base of the cancer with an electric needle.  
  C and E might be an option for treating small basal cell carcinomas that are less likely to recur, such as those that form on the back, chest, hands and feet.
* **Radiation therapy.** Radiation therapy uses high-energy beams, such as X-rays and protons, to kill cancer cells.  
  Radiation therapy is sometimes used after surgery when there is an increased risk that the cancer will return. It might also be used when surgery isn't an option.
* **Freezing.** This treatment involves freezing cancer cells with liquid nitrogen (cryosurgery). It may be an option for treating superficial skin lesions. Freezing might be done after using a scraping instrument (curet) to remove the surface of the skin cancer.  
  Cryosurgery might be considered for treating small and thin basal cell carcinomas when surgery isn't an option.
* **Topical treatments.** Prescription creams or ointments might be considered for treating small and thin basal cell carcinomas when surgery isn't an option.
* **Photodynamic therapy.** Photodynamic therapy combines photosensitizing drugs and light to treat superficial skin cancers. During photodynamic therapy, a liquid drug that makes the cancer cells sensitive to light is applied to the skin. Later, a light that destroys the skin cancer cells is shined on the area.  
  Photodynamic therapy might be considered when surgery isn't an option.

### **Treatment for cancer that spreads**

Very rarely, basal cell carcinoma may spread (metastasize) to nearby lymph nodes and other areas of the body. Additional treatment options in this situation include:

* **Targeted drug therapy.** Targeted drug treatments focus on specific weaknesses present within cancer cells. By blocking these weaknesses, targeted drug treatments can cause cancer cells to die.  
  Targeted therapy drugs for basal cell carcinoma block molecular signals that enable the cancers to continue growing. They might be considered after other treatments or when other treatments aren't possible.
* **Chemotherapy.** Chemotherapy uses powerful drugs to kill cancer cells. It might be an option when other treatments haven't helped.

## **TNM Categories for Basal Cell Carcinoma**

T (Tumor) Categories:

* TX: Primary tumor cannot be assessed
* Tis: Carcinoma in situ (confined to the epidermis)
* T1: Tumor ≤ 2 cm in greatest dimension
* T2: Tumor > 2 cm but ≤ 4 cm
* T3: Tumor > 4 cm or minor bone erosion, perineural invasion, or deep invasion
* T4: Tumor with gross cortical bone/marrow invasion or skull base involvement
  + T4a: Gross cortical bone/marrow invasion
  + T4b: Skull base invasion and/or skull base foramen involvement

N (Lymph Nodes) Categories:

* NX: Regional lymph nodes cannot be assessed
* N0: No regional lymph node metastasis
* N1: Metastasis in a single ipsilateral lymph node ≤ 3 cm without extranodal extension (ENE)
* N2: More extensive nodal involvement or ENE positive nodes (subcategories N2a, N2b, N2c)
* N3: Metastasis in lymph node > 6 cm or with extranodal extension (subcategories N3a, N3b)

M (Metastasis) Categories:

* M0: No distant metastasis
* M1: Distant metastasis present

## 

## **Basal Cell Carcinoma (BCC) Treatment: Drug Information and Side Effects**

## 1. Topical Medications

These are mainly used for superficial or low-risk BCCs, especially when surgery is not preferred.

* 5-Fluorouracil (5-FU) (Brand names: Efudex®, Carac®, Fluoroplex®, Tolak®)
  + Mechanism: Topical chemotherapy that inhibits cell growth and promotes cancer cell death.
  + Use: FDA-approved for superficial BCCs; cure rates around 80–90%.
  + Side effects: Local skin reactions such as redness, irritation, burning, itching, crusting, and sometimes ulceration at the application site. These effects usually resolve after treatment ends.
* Imiquimod (Brand names: Aldara®, Zyclara®)
  + Mechanism: Immune response modifier that stimulates the body’s immune system to attack cancer cells.
  + Use: Approved for superficial BCCs with similar cure rates (82–90%).
  + Side effects: Local inflammation, redness, swelling, erosion, and sometimes flu-like symptoms due to immune activation.
* Diclofenac gel and Ingenol mebutate gel
  + Occasionally used for superficial lesions but less common for BCC. Side effects are similar local skin irritation.

## 2. Oral Hedgehog Pathway Inhibitors

Used for advanced, metastatic, or inoperable BCC.

* Vismodegib (Erivedge®) and Sonidegib (Odomzo®)
  + Mechanism: Inhibit the Hedgehog signaling pathway, which is abnormally activated in BCC.
  + Use: For locally advanced or metastatic BCC not suitable for surgery or radiation.
  + Side effects: Muscle spasms, hair loss, taste disturbances, weight loss, fatigue, nausea, diarrhea, and potential birth defects (contraindicated in pregnancy).

## 3. Immunotherapy

* Cemiplimab (Libtayo®)
  + Mechanism: PD-1 inhibitor used in advanced BCC resistant to Hedgehog inhibitors.
  + Side effects: Fatigue, rash, diarrhea, immune-related adverse effects such as pneumonitis or colitis.

## 4. Other Treatments

* Topical chemotherapy agents are generally second-line to surgery but useful when surgery is contraindicated or refused.
* Surgical excision remains the gold standard with the lowest recurrence rates.

## 

## **Diagnostic Considerations**

Although basal cell carcinoma rarely metastasizes, a tumor can extend beneath the skin to the bone, causing considerable local damage due to tissue destruction. This process leads to an ulcer that is sometimes known as *ulcus rodens,* or a rodent ulcer.

Other medical problems/issues to consider include the following:

* Dermatitis
* Desmoplastic trichoepithelioma
* Eczema
* Intradermal nevus
* Lichenoid benign keratosis
* Ringworm
* Fibroepithelioma of Pinkus
* Adnexal carcinoma (very rare)
* Actinic keratosis
* Sebaceous hyperplasia
* Nevi malignant melanoma
* Keratoacanthoma
* Seborrheic keratosis
* Bowen disease
* Darier disease (keratosis follicularis)
* Metastatic malignancies

## 

## **Differential Diagnoses**

* Actinic Keratosis
* Bowen Disease
* Cutaneous T-Cell Lymphoma
* Fibrous Papule of the Face
* Juvenile Nasopharyngeal Angiofibroma
* Malignant Melanoma
* Melanocytic Nevi
* Molluscum Contagiosum
* Psoriasis
* Sebaceous Hyperplasia
* Trichoepithelioma

## 

## **Complications**

Complications of basal cell carcinoma can include:

* **A risk of recurrence.** Basal cell carcinomas commonly recur, even after successful treatment.
* **An increased risk of other types of skin cancer.** A history of basal cell carcinoma may also increase the chance of developing other types of skin cancer, such as squamous cell carcinoma.
* **Cancer that spreads beyond the skin.** Very rarely, basal cell carcinoma can spread (metastasize) to nearby lymph nodes and other areas of the body, such as the bones and lungs.

## 

## **Prevention**

To reduce your risk of basal cell carcinoma you can:

* **Avoid the sun during the middle of the day.** In many places, the sun's rays are strongest between about 10 a.m. and 4pm Schedule outdoor activities for other times of the day, even during winter or when the sky is cloudy.
* **Wear sunscreen year-round.** Use a broad-spectrum sunscreen with an SPF of at least 30, even on cloudy days. Apply sunscreen generously, and reapply every two hours — or more often if you're swimming or perspiring.
* **Wear protective clothing.** Cover your skin with dark, tightly woven clothing that covers your arms and legs, and a broad-brimmed hat, which provides more protection than does a baseball cap or visor.  
  Some companies also sell protective clothing. A dermatologist can recommend an appropriate brand. Don't forget sunglasses. Look for those that block both types of Ultraviolet (UV) radiation — Ultraviolet A (UVA) and Ultraviolet B (UVB) rays.
* **Avoid tanning beds.** Tanning beds emit UV rays and can increase your risk of skin cancer.
* **Check your skin regularly and report changes to your doctor.** Examine your skin often for new skin growths or changes in existing moles, freckles, bumps and birthmarks. With the help of mirrors, check your face, neck, ears and scalp.  
  Examine your chest and trunk and the tops and undersides of your arms and hands. Examine both the front and the back of your legs and your feet, including the soles and the spaces between your toes. Also check your genital area and between your buttocks.

## 

## **Epidemiology**

The American Cancer Society (ACS) reports skin cancer as being the most common cancer in the United States, with basal cell carcinoma (BCC) constituting the majority of cases. The ACS cites an estimate that about 5.4 million basal and squamous cell skin cancers are diagnosed each year in about 3.3 million persons in the US, with about 80% of those being BCCs. Although the number of these skin cancers has been increasing for years, death from them remains uncommon: non-melanoma skin cancers are estimated to cause about 2000-8000 deaths annually (mostly from squamous cell skin cancers), and that number has been decreasing in recent years.

The estimated lifetime risk for BCC in the White population is 33-39% for men and 23-28% for women. BCC incidence doubles every 25 years.

In the US states near the equator, such as Hawaii, BCC incidence is approaching three-fold that of states in the Midwest, such as Minnesota. BCC incidence also varies globally. The highest rates of skin cancer occur in South Africa and Australia, areas that receive high amounts of UV radiation.Australia has a trend toward increasing BCC incidence, while Finland has a low reported incidence that is approximately one quarter that in Minnesota; BCC incidence in Finland also appears to be increasing, however, especially among young women.

BCC is the least likely cancer to metastasize. BCC differs from squamous cell carcinoma, which accounts for 16% of skin cancers and is more life-threatening.

### Race

Although BCC is observed in people of all races and skin types, dark-skinned individuals are rarely affected; BCC is most often found in light-skinned individuals (type 1 or type 2 skin). Those with type 1 skin are very fair and have red or blond hair and freckles; these individuals always burn and never tan. Those with type 2 skin are fair and burn easily while tanning minimally. Whites of Celtic ancestry have the highest risk for BCC. Incidence is low in persons with type 5 and 6 skin.

### Sex

Historically, men are affected twice as often as women. The higher incidence in men is probably due to increased recreational and occupational exposure to the sun, although these differences are becoming less significant with changes in lifestyle. The current male-to-female ratio is approximately 2.1:1.

For tumors involving the periocular skin, Cook et al reported the incidence of BCC to be equal in men and women.In addition, this investigative team found that the age-adjusted incidence rates for all malignant tumors of the eyelid in men and women, respectively, were 19.6 cases and 13.3 cases per 100,000 population per year. The age-adjusted incidence rates for BCC of the eyelid for men and women, respectively, were 16.9 and 12.4 cases per 100,000 population per year.

### Age

The likelihood of developing BCC increases with age. Data indicate that BCC incidence is far higher (more than 100-fold) in persons aged 55-70 years than in those aged 20 years and younger. Patients 50-80 years of age are affected most often. The median age at diagnosis is 67 years and the mean age is 64 years.

Nevertheless, BCC can develop in teenagers and appears frequently in fair-skinned patients aged 30-50 years. Approximately 5% to 15% of cases of BCC occur in patients aged 20-40 years. Aggressive-growth types of BCC are more frequently noted in patients younger than 35 years than in older individuals.

Zhang et al reported an inverse association between body mass index (BMI) and onset of BCC before age 40 years. The multivariate odds ratio for early-onset BCC in obese versus normal individuals was 0.43 for adult BMI and 0.54 for BMI at age 18.

**Recommendations**

* Clinicians should counsel young adults, adolescents, children, and parents of young children about minimizing exposure to ultraviolet (UV) radiation for persons aged 6 months to 24 years with fair skin types to reduce their risk of skin cancer.
* Clinicians should selectively offer counseling to adults older than 24 years with fair skin types about minimizing their exposure to UV radiation to reduce risk of skin cancer. Counseling all adults older than 24 years offers only small benefit. In determining whether counseling is appropriate in individual cases, patients and clinicians should consider the presence of risk factors for skin cancer.
* Current evidence is insufficient to assess the balance of benefits and harms of counseling adults about skin self-examination to prevent skin cancer.

**Specific recommendations for pediatricians include the following**

* Health-supervision practices should include advice about UVR exposure, such as avoiding sunburn and suntan, wearing clothing and hats with brims, using sunglasses, and applying sunscreen; if possible, outdoor activities should be scheduled to limit exposure to peak-intensity midday sun (10 am to 4 pm).
* When a child or adolescent might sunburn, he or she should use sunscreen to reduce the known risks for sun exposure and sunburn, including the increased risk for skin cancer. Sunscreen with a sun-protection factor (SPF) of at least 15 should be applied every 2 hours and after swimming, sweating, or drying off with a towel. People may prefer to avoid sunscreens containing oxybenzone, as these may have weak estrogenic effects when absorbed through the skin.
* Although all children need counseling about UVR exposure, this is particularly true for children at high risk for the development of skin cancer, including those with light skin, nevi, and/or freckling; and/or a family history of melanoma.
* Skin cancer prevention is a lifelong effort, and beginning in infancy, at least one health maintenance visit per year should include advice about UVR exposure. All children are at risk for adverse effects of UVR exposure on the eyes and immune system, although not all children sunburn. Especially appropriate times for counseling about UVR exposure include during the spring and summer in northern states, before anticipated sunny vacations, and during visits for sunburns.
* Because outdoor physical activity should be strongly encouraged, this should be promoted in a sun-safe manner.
* Sun-protection practices tend to wane in early childhood. Beginning at age 9 or 10 years, it may be helpful for pediatricians to discuss sun protection with children, together with parents, to encourage joint responsibility for the child's sun protection.
* Infants younger than 6 months should be kept out of direct sunlight and covered with protective clothing and hats. When sun avoidance is impossible, parents may apply sunscreen only on exposed areas. Absorption of sunscreen ingredients may be higher in preterm infants.
* Pediatricians should become familiar with chemical photosensitizing agents. People using these oral or topical agents should limit sun exposure and avoid all ultraviolet A (UVA) light from artificial sources. When sun exposure is inevitable, they should wear fully protective clothing and high-SPF sunscreen that also blocks UVA wavelengths.
* Breast-fed and formula-fed infants and other children should receive vitamin D supplementation in accordance with guidelines, for a total intake of at least 400 IU of vitamin D daily. Children at risk for hypovitaminosis D may need laboratory testing of 25-hydroxyvitamin D concentration.
* Deliberate UVR exposure to artificial sources and overexposure to sun with the goal of increasing vitamin D concentrations or for other reasons should be avoided.
* Pediatricians should advocate for adoption of sun-protective policies (eg, shaded playgrounds, outdoor time before 10 am, and allowing hats at schools and child care facilities).
* Pediatricians should support and advocate for legislation banning use of tanning parlors by children younger than 18 years.

**For all individuals, regardless of age, the ACS recommends the following**

* Staying in the shade when outdoors
* Wearing protective clothing when out in the sun
* Wearing a hat that shades your face, neck, and ears
* Wearing a broad-spectrum sunscreen with an SPF of at least 30
* Planning outdoor activities to avoid the midday sun
* Wearing wrap-around sunglasses that block at least 99% of UV light
* Avoiding tanning beds and sunlamps

### Skin Cancer Screening

The USPSTF did note the following clinical considerations:

* Skin cancer of any type occurs more commonly in men than in women and among persons with a fair complexion, persons who use indoor tanning beds, and persons with a history of sunburns or previous skin cancer.
* Basal and squamous cell carcinomas are the most common types of skin cancer but infrequently lead to death or substantial morbidity.

**QUESTION AND ANSWER SET**

## Do I have skin cancer? What kind?

If your doctor has diagnosed you with basal cell carcinoma, it means you have the most common type of skin cancer that starts in the basal cells of your skin. It often appears as a shiny, pearly bump or a scaly patch that doesn’t heal, usually on sun-exposed areas like your face or neck

## 2. How is this type of skin cancer different from other types?

BCC grows slowly and rarely spreads (metastasizes) to other parts of the body, unlike melanoma or squamous cell carcinoma. However, it can invade nearby tissues and cause damage if untreated. It usually remains localized but can be locally aggressive

## 3. Has my cancer spread?

Most basal cell carcinomas do not spread. Metastasis is extremely rare. Your doctor will determine if it has spread by physical examination and possibly imaging or biopsy. If the cancer is large, recurrent, or aggressive, further tests may be done to check for spread

## 4. What treatment approach do you recommend?

Treatment depends on the size, location, and subtype of your BCC. Common treatments include:

* Surgical excision (cutting out the tumor)
* Mohs micrographic surgery for precise removal with minimal tissue loss
* Topical treatments like 5-fluorouracil or imiquimod for superficial BCC
* Cryotherapy or photodynamic therapy for some superficial lesions
* For advanced cases, targeted drugs like hedgehog pathway inhibitors or immunotherapy may be used

## 5. What are the possible side effects of this treatment?

* Surgery may cause pain, bleeding, infection, and scarring.
* Topical treatments can cause redness, irritation, and inflammation at the application site.
* Targeted drugs may cause muscle spasms, taste changes, fatigue, and other systemic effects.
* Mohs surgery generally has fewer side effects and preserves healthy tissue

## 6. Will I have a scar after treatment?

Yes, most treatments, especially surgical ones, will leave a scar. The size and appearance depend on the tumor size and location and the surgical technique used. Mohs surgery aims to minimize scarring

## 7. Am I at risk of this condition recurring?

Yes, BCC can recur, especially if not completely removed. The risk is higher for larger tumors, aggressive subtypes, or if located in high-risk areas like the nose or ears. Regular follow-up is important to detect recurrences early

## 8. Am I at risk of other types of skin cancer?

Yes, having BCC increases your risk of developing other skin cancers, including squamous cell carcinoma and melanoma. Sun protection and regular skin checks are essential

## 9. How often will I need follow-up visits after I finish treatment?

Follow-up schedules vary but typically involve skin exams every 6 to 12 months for several years, as new lesions or recurrences can develop. Your doctor will tailor the plan based on your risk factors

## 10. Are my family members at risk of skin cancer?

Skin cancer risk depends on genetic, environmental, and lifestyle factors. Family members with fair skin, a history of sunburns, or extensive sun exposure may have higher risk. Encourage them to practice sun safety and get regular skin checks

## **Genomic Features of Basal Cell Carcinoma**

* High Mutation Rate:  
  BCC exhibits one of the highest mutation rates among human cancers, with over 65 mutations per megabase (Mbp), largely due to ultraviolet (UV) radiation exposure
* Hedgehog Pathway Mutations:  
  The majority (~75–90%) of BCCs harbor mutations in genes regulating the HH pathway, which controls cell growth and differentiation:
  + PTCH1: The most frequently mutated gene (up to 75%), usually loss-of-function mutations that prevent PTCH1 from inhibiting SMO, leading to uncontrolled pathway activation
  + SMO: Activating mutations found in 10–20% of cases, leading to constitutive pathway activation
  + SUFU and PTCH2: Less commonly mutated HH pathway components (~8% for SUFU)
* Tumor Suppressor TP53:  
  Mutations in the *TP53* gene occur in approximately 45–61% of BCCs. These are often UV-signature mutations affecting the tumor suppressor function, contributing to carcinogenesis
* Non Coding Region Mutations:  
  Around 50% of mutations in BCC occur in noncoding regions (e.g., 5’UTRs, 3’UTRs), affecting gene regulation. Hotspots have been identified in genes like *BAD*, *DHODH*, and *CHCHD2*, which are involved in apoptosis, metabolism, and UV-induced cancer pathways
* Copy Number Alterations:  
  Frequent deletions of chromosome 9q (encompassing *PTCH1*) and gains in 9p (including immune checkpoint genes PD-L1 and PD-L2) have been reported, suggesting roles in tumor progression and immune evasion
* Other Mutated Genes:  
  Studies, including one on Korean patients, identified additional mutations in *LRP1B*, *ROS1*, *KMT2C*, *NSD1*, *ARID1A*, *NOTCH1/2*, *FAT1/4*, *ERBB4*, and *GRIN2A*, with some variation between high-risk and low-risk BCC subtypes
* TERT Promoter Mutations:  
  Mutations in the *TERT* promoter region, which regulate telomerase activity, are found in a significant proportion (~58%) of BCC lesions, contributing to cellular immortality

**Doctor-patient conversation about Basal Cell Carcinoma (BCC)**

Doctor:  
“Hello, I’ve reviewed your skin lesion and the biopsy results confirm it’s basal cell carcinoma, which is the most common type of skin cancer.”

Patient:  
“What exactly is basal cell carcinoma? Is it serious?”

Doctor:  
“Basal cell carcinoma usually grows slowly and rarely spreads to other parts of the body. However, if left untreated, it can grow deeper into the skin and nearby tissues, causing damage. Early treatment is very effective.”

Patient:  
“How did I get this? And where does it usually occur?”

Doctor:  
“It most often develops on areas exposed to the sun, like your face, neck, or shoulders. It’s mainly caused by long-term sun exposure and UV damage.”

Patient:  
“What are my treatment options?”

Doctor:  
“For most cases, we remove the tumor surgically, which is usually curative. Depending on the size and location, we might use Mohs surgery to remove the cancer precisely while sparing healthy tissue. For superficial lesions, topical treatments or photodynamic therapy may be options. If the tumor is large or in a difficult location, we might consider other treatments.”

Patient:  
“Will I have a scar? How big will it be?”

Doctor:  
“There will be a scar after surgery, but we aim to minimize it, especially on visible areas like the face. Mohs surgery often results in smaller scars compared to traditional excision.”

Patient:  
“Can this cancer come back? Will I get other skin cancers?”

Doctor:  
“Basal cell carcinomas can recur, so regular follow-up is important. Also, having one BCC increases your risk of developing others, so we recommend regular skin checks and sun protection.”

Patient:  
“How often will I need to come back for follow-up?”

Doctor:  
“Typically, we see patients every 6 to 12 months for a full skin examination to catch any new or recurring lesions early.”

Patient:  
“Is there anything I can do to prevent this from happening again?”

Doctor:  
“Absolutely. Avoid excessive sun exposure, use broad-spectrum sunscreen daily, wear protective clothing, and avoid tanning beds. Checking your skin regularly and reporting any new or changing spots promptly is also very important.”

Patient:  
“Thank you. Is there any information I can take home?”

Doctor:  
“Yes, I’ll give you some brochures and reliable website links to learn more about basal cell carcinoma, treatment options, and skin cancer prevention.”

REFERENCES

<https://emedicine.medscape.com/article/276624-guidelines>

[Basal cell carcinoma - Symptoms & causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/basal-cell-carcinoma/symptoms-causes/syc-20354187)

**SQUAMOUS CELL CARCINOMA(SKIN)**

**DEFINITION AND DESCRIPTION**

Squamous cell carcinoma of the skin is a type of cancer that starts as a growth of cells on the skin. It starts in cells called squamous cells. The squamous cells make up the middle and outer layers of the skin. Squamous cell carcinoma is a common type of skin cancer.

Squamous cell carcinoma of the skin is usually not life-threatening. But if it's not treated, squamous cell carcinoma of the skin can grow large or spread to other parts of the body. The growth of the cancer can cause serious complications.

Most squamous cell carcinomas of the skin are caused by too much ultraviolet (UV) radiation. UV radiation comes either from sunlight or from tanning beds or lamps. Protecting your skin from UV light can help reduce the risk of squamous cell carcinoma of the skin and other forms of skin cancer.

Squamous cell carcinomas can be anywhere on the skin. In people who sunburn easily, the cancer is usually found on areas of skin that have had a lot of sun. In people with Black and brown skin, squamous cell carcinomas are more likely to be on skin that isn't exposed to sun, such as the genitals.

**CAUSES**

Squamous cell carcinoma of the skin occurs when the squamous cells in the skin get changes in their DNA. Cells' DNA holds the instructions that tell cells what to do. The changes tell the squamous cells to multiply quickly. The cells continue living when healthy cells would die as part of their natural life cycle.

This causes too many cells. The cells can invade and destroy healthy body tissue. In time, the cells can break away and spread to other parts of the body.

Ultraviolet (UV) radiation causes most of the DNA changes in skin cells. UV radiation can come from sunlight, tanning lamps and tanning beds.

But skin cancers also can grow on skin that's not usually in sunlight. This means that other factors might add to the risk of skin cancer. One such factor might be having a condition that weakens the immune system.

**Risk factors**

Factors that can increase the risk of squamous cell carcinoma of the skin include:

* **Having skin that sunburns easily.** Anyone of any skin color can get squamous cell carcinoma of the skin. But it's more common in people who have low levels of melanin in their skin. Melanin is a substance that gives color to skin. It also helps protect the skin from damaging ultraviolet (UV) radiation. People with Black or brown skin have more melanin than people with white skin.  
  The risk of squamous cell carcinoma is highest in people who have blond or red hair, have light-colored eyes and freckle or sunburn easily.
* **Being in the sun too much.** UV radiation from the sun increases the risk of squamous cell carcinoma of the skin. Covering the skin with clothes or sunblock can help lower the risk.
* **Using tanning beds.** People who use indoor tanning beds have an increased risk of squamous cell carcinoma of the skin.
* **Having a history of sunburns.** Having had one or more sunburns that raised blisters as a child or teenager increases the risk of developing squamous cell carcinoma of the skin as an adult. Sunburns in adulthood also are a risk factor.
* **Having a history of precancerous skin lesions.** Some types of skin sores can turn into skin cancer. Examples are actinic keratosis or Bowen disease. Having one of these conditions increases the risk of squamous cell carcinoma.
* **Having a history of skin cancer.** People who've had squamous cell carcinoma of the skin once are much more likely to get it again.
* **Having a weakened immune system.** People with weakened immune systems have an increased risk of skin cancer. This includes people who have leukemia or lymphoma. And it includes those who take medicines to control the immune system, such as those who have had organ transplants.
* **Having a rare genetic disorder.** People with xeroderma pigmentosum, which causes great sensitivity to sunlight, have a greatly increased risk of developing skin cancer.
* **Having human papillomavirus infection (HPV).** This common infection that's passed through sexual contact increases the risk of squamous cell carcinoma of the skin.
* **Having scars or long-lasting wounds on the skin.** Squamous cell carcinoma of the skin can form in scars, burns and sores that don't heal.

**Symptoms**

Squamous cell carcinoma of the skin most often occurs on sun-exposed skin. This includes the scalp, the backs of the hands, the ears or the lips. But it can occur anywhere on the body. It can even occur inside the mouth, on the bottoms of the feet or on the genitals. When squamous cell carcinoma of the skin happens in people with Black and brown skin, it tends to happen in places that aren't exposed to the sun.

Symptoms of squamous cell carcinoma of the skin include:

* A firm bump on the skin, called a nodule. The nodule might be the same color as the skin, or it might look different. It can look pink, red, black or brown, depending on skin color.
* A flat sore with a scaly crust.
* A new sore or raised area on an old scar or sore.
* A rough, scaly patch on the lip that may become an open sore.
* A sore or rough patch inside the mouth.
* A raised patch or wart like sore on or in the anus or on the genitals.

### 

### **When to see a doctor**

Make an appointment with a healthcare professional for a sore or scab that doesn't heal in about two months or a flat patch of scaly skin that won't go away.

## **Diagnosis**

Tests and procedures used to diagnose squamous cell carcinoma of the skin include:

* **Physical exam.** A member of your health care team asks about your health history and looks at your skin for signs of squamous cell carcinoma of the skin.
* **Removing a sample of tissue for testing, called a biopsy.** A biopsy is a procedure to remove a sample of tissue for testing in a lab. A member of your health care team uses a tool to cut away, shave off or punch out some or all of the area of skin that looks unusual. The sample is tested in a lab to see if it is cancer.

**Treatment**

Most squamous cell carcinomas of the skin can be removed with minor surgery. Some are removed with a medicine applied to the skin. The treatment depends on where the cancer is, how large it is, how fast it's growing and what you prefer.

### **Treatments for very small skin cancers**

If the skin cancer is small, not deep into the skin, called superficial, and has a low risk of spreading, less-invasive treatment choices include:

* **Curettage and electrodessication.** This treatment involves removing the top of the skin cancer with a scraping tool called a curet. Then an electric needle is used to sear the base of the cancer.
* **Laser therapy.** This treatment uses an intense beam of light to destroy growths. There's usually little damage to nearby tissue. And there's a reduced risk of bleeding, swelling and scarring.
* **Freezing.** This treatment, called cryosurgery, involves freezing cancer cells with liquid nitrogen. Freezing might be done after using a scraping tool, called a curet, to remove the surface of the skin cancer.
* **Photodynamic therapy.** During photodynamic therapy, a liquid medicine that makes the cancer cells sensitive to light is applied to the skin. Later, a light that destroys the skin cancer cells is shined on the area. This treatment might be used with surgery or other treatments.

### **Treatments for larger skin cancers**

More-invasive treatments might be recommended for larger squamous cell carcinomas and those that go deeper into the skin. Options might include:

* **Simple excision.** This involves cutting out the cancer and a margin of healthy skin around it. Sometimes more skin around the tumor is removed, called a wide excision.
* **Mohs surgery.** Mohs surgery involves removing the cancer layer by layer and looking at each layer under the microscope until no cancer cells are left. This allows the surgeon to remove the whole growth without taking too much of the healthy skin around it.
* **Radiation therapy.** Radiation therapy uses powerful energy beams to kill cancer cells. Radiation therapy is sometimes used after surgery when there is an increased risk that the cancer might return. It also might be an option for people who can't have or don't want surgery.

### **Treatments for skin cancer that spreads past the skin**

When squamous cell carcinoma spreads to other parts of the body, medicines might be recommended, including:

* **Chemotherapy.** Chemotherapy uses strong medicines to kill cancer cells. If squamous cell carcinoma spreads to the lymph nodes or other parts of the body, chemotherapy can be used alone or with other treatments, such as targeted therapy and radiation therapy.
* **Targeted therapy.** Targeted therapy uses medicines that attack specific chemicals in the cancer cells. By blocking these chemicals, targeted treatments can cause cancer cells to die. Targeted therapy is usually used with chemotherapy.
* **Immunotherapy.** Immunotherapy is a treatment with medicine that helps the body's immune system kill cancer cells. The immune system fights off diseases by attacking germs and other cells that shouldn't be in the body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells.  
  For squamous cell carcinoma of the skin, immunotherapy might be considered when the cancer is advanced and other treatments aren't an option.

# 

# **Non-surgical Local Treatment for Squamous Cell Skin Cancers**

Cryotherapy, photodynamic therapy, topical chemotherapy, or other local treatments might be options to treat basal and squamous cell skin cancers (or pre-cancers) that haven't spread beyond the skin.

These are called local treatments because they only affect the area being treated. Some of these techniques might be described as types of surgery because they destroy a targeted area of body tissue. But these techniques are different from surgery because they don’t use scalpels or cut into the skin. (Radiation therapy is also a type of local treatment.)

## **Cryotherapy (cryosurgery)**

Cryotherapy is used most often for precancerous skin conditions such as actinic keratosis. It might also be used for squamous cell carcinoma in situ (Bowen disease) or for small basal cell and squamous cell carcinomas.

For this treatment, the doctor applies liquid nitrogen to the tumor to freeze and kill the cells. This is often repeated a couple of times in the same office visit.

After the dead area of skin thaws, it will swell, blister and crust over. The treated area may have fluid draining from it for a while, and it might take a month or two to heal. It will leave a scar, and the area might have less color after treatment.

## **Photodynamic therapy (PDT)**

PDT can be used to treat actinic keratoses. It might also be an option to treat some small, low risk basal cell skin cancers, as well as very early forms of squamous cell cancer (known as squamous cell carcinoma in situ, or Bowen disease).

For this treatment, a drug is applied to the skin as a gel or liquid. The drug collects in the tumor cells over several hours, where it is converted to a different chemical that makes the cells very sensitive to certain types of light. A special light source is then focused on the tumor(s), which kills the cells. Another option to activate the drug, especially when large areas need to be treated, is to have the person go out into the sunlight for a specific amount of time (known as daylight PDT).

PDT can cause redness and swelling on the skin where it is used. Another possible side effect of PDT is that it can make a person’s skin very sensitive to sunlight for some time, so precautions may be needed to avoid severe burns.

## **Topical chemotherapy**

Chemotherapy (chemo) uses drugs that kill cancer cells. Topical chemotherapy means that an anti-cancer medicine is put directly on the skin (usually in a cream or ointment) rather than being taken by mouth or given as an IV into a vein.

**5-fluorouracil (5-FU)**: The drug most often used in topical treatment of actinic keratoses, as well as some basal and squamous cell skin cancers, is 5-FU (with brand names such as Efudex, Carac, and Fluoroplex). It is typically applied to the skin once or twice a day for several weeks. Sometimes it might be used along with calcipotriol (calcipotriene), a drug related to vitamin D, which could shorten the length of treatment to days instead of weeks.

When put directly on the skin, 5-FU kills tumor cells on or near the skin’s surface, but it can’t reach cancer cells deeper in the skin or those that have spread to other parts of the body. For this reason, topical 5-FU is generally used only for precancerous conditions such as actinic keratosis and for some very superficial skin cancers (cancers that only affect the surface of the skin).

Because the drug is only applied to the skin, it doesn’t spread throughout the body, so it doesn’t cause the same side effects as systemic chemotherapy (treatment that affects the whole body). But it does make the treated skin red and very sensitive for a few weeks. Other topical medicines can be used to help relieve this, if needed. 5-FU can also make the skin more sensitive to sunlight, so treated areas must be protected from the sun to prevent sunburn for a few weeks after treatment.

A very small portion of people have a condition called DPD deficiency, which makes it hard for their bodies to break down and get rid of 5-FU. This can result in serious or even life-threatening side effects. If you are applying 5-FU and have any reactions beyond those you were told to expect on your skin, call your doctor or nurse right away.

**Tirbanibulin (Klisyri**): This chemo drug comes in an ointment that can be used to treat actinic keratoses on the face or scalp. It is usually applied to the skin once a day for 5 days. It’s important to avoid getting this drug in or near your eyes or mouth.

The most common side effects of this drug include itching or pain in the treatment area. Some people might have more serious skin reactions, such as severe redness or swelling in the area, flaking, scaling, peeling, or crusting of the skin, blisters, pus, sores, or breakdown of the skin.

**Diclofenac (Solaraze)**: A gel containing the drug diclofenac is sometimes used to treat actinic keratoses. This drug is part of a group of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs), which includes aspirin and ibuprofen. The gel is usually applied twice daily for 2 or 3 months. It may cause less severe skin reactions than the chemo drugs above, but it can also take longer to work.

## **Immune response modifiers**

Some drugs can boost the body’s immune response against the cancer, causing it to shrink and go away.

Imiquimod (Zyclara) is a cream that can be applied to actinic keratoses and some very early basal cell cancers. It causes the immune system to react to the skin lesion and destroy it. It’s typically applied at least a few times a week for several weeks, although schedules can vary. Like other topical products, it can cause severe skin reactions in some people. It can also cause flu-like symptoms.

## **Laser surgery**

This approach uses a beam of laser light to destroy the top layers of the skin. It might be an option for actinic keratosis, squamous cell carcinoma in situ (Bowen disease), or for very superficial basal cell cancers (those only on the surface of the skin). It’s not yet known if this type of treatment is as effective as standard methods of treatment, and it’s not widely used.

## **Chemical peeling**

For this treatment, the doctor applies a chemical such as trichloroacetic acid (TCA) to the skin tumor, killing the tumor cells. This can lead to redness and peeling of the skin over the course of several days. This approach is sometimes used to treat actinic keratosis.

## **Staging**

### TNM staging system

Like many cancers, cSCC is classified according to the American Joint Committee on Cancer (AJCC)/International Union against Cancer (UICC) tumor-node-metastasis (TNM) staging system. This anatomy-based staging system is designed to stratify patients into general prognostic cohorts based on the size and extent of disease.

The TNM staging system for nonmelanoma skin cancers, including cSCC, is as follows (see also Table 1, below)

*Primary tumor (T)*

* TX: Primary tumor cannot be assessed
* T0: No evidence of primary tumor
* Tis: Carcinoma in situ
* T1: Tumor 2 cm or less that has fewer than 2 high-risk features
* T2: Tumor larger than 2 cm or tumor of any size with 2 or more high-risk features
* T3: Tumor with invasion of maxilla, mandible, orbit, or temporal bone
* T4: Tumor with invasion of axial or appendicular skeleton or perineural invasion of the skull base

High-risk features include the following:

* Thickness >2 mm
* Clark level 4 or higher
* Perineural invasion
* Ear as primary site
* Hair-bearing lip as primary site
* Poorly differentiated histology

*Regional lymph nodes (N)*

* NX: Regional lymph nodes cannot be assessed
* N0: No regional lymph node metastasis
* N1: Single ipsilateral lymph node metastases ≤3 cm in greatest dimension
* N2a: Metastasis in a single ipsilateral lymph node and >3 cm, but ≤6 cm in greatest dimension
* N2b: Metastasis in multiple ipsilateral lymph nodes and ≤6 cm in greatest dimension
* N2c: Metastasis in bilateral or contralateral lymph nodes and ≤6 cm in greatest dimension
* N3: Metastasis in a lymph node and >6 cm in greatest dimension

*Distant metastasis (M)*

* MX: Distant metastasis cannot be assessed
* M0: No distant metastasis
* M1: Distant metastasis

**Table 1. Stage Grouping**

| Stage | Primary Tumor | Regional Lymph Nodes | Distant Metastasis |
| --- | --- | --- | --- |
| Stage 0 | Tis | N0 | M0 |
| Stage I | T1 | N0 | M0 |
| Stage II | T2 | N0 | M0 |
| Stage III | T3 | N0 | M0 |
| T1-3 | N1 | M0 |
| Stage IV | T4 | N0 | M0 |
| Any T | N2-3 | M0 |
| Any T | Any N | M1 |

### N1S3 staging system

The stages of N1S3 are as follows:

* Stage I - A single lymph node measuring 3 cm or less
* Stage II - A single lymph node greater than 3 cm, or multiple lymph nodes measuring 3 cm or less
* Stage III - Multiple lymph nodes greater than 3 cm

The N1S3 system was found to have a significant predictive capacity for locoregional control, disease-specific survival, and overall survival in a group of 215 patients. Testing in a different cohort of 250 patients provided validation of its predictive capacity.

**Complications**

Untreated squamous cell carcinoma of the skin can destroy nearby healthy tissue. It can spread to the lymph nodes or other organs. And it can be fatal, although this is not common.

The risk of squamous cell carcinoma of the skin spreading may be higher if the cancer:

* Grows very large or deep.
* Involves the mucous membranes, such as the lips.
* Occurs in a person with a weakened immune system. Examples of things that might cause a weakened immune system include having chronic leukemia or taking medicine to control the immune system after an organ transplant.

**Prevention**

Most squamous cell carcinomas of the skin can be prevented. To protect yourself:

* **Stay out of the sun during the middle of the day.** For much of North America, the sun's rays are strongest between about 10 a.m. and 3 p.m. Plan outdoor activities at other times of the day, even during winter or when the sky is cloudy. When outside, stay in shade as much as possible.
* **Wear sunscreen year-round.** Use a broad-spectrum sunscreen with an SPF of at least 30, even on cloudy days. Apply sunscreen generously. Apply again every two hours, or more often if you're swimming or sweating.
* **Wear protective clothing.** Wear dark, tightly woven clothes that cover arms and legs. Wear a wide-brimmed hat that shades your face and ears. Don't forget sunglasses. Look for those that block both types of UV radiation, UVA and UVB rays.
* **Don't use tanning beds.** The lights in tanning beds give off UV radiation. Using tanning beds increases the risk of skin cancer.
* **Check your skin often and report changes to your health care team.** Look at your skin often for new growths. Look for changes in moles, freckles, bumps and birthmarks. Use mirrors to check your face, neck, ears and scalp.  
  Look at your chest and trunk and the tops and undersides of your arms and hands. Look at the front and back of your legs and your feet. Look at the bottom of the feet and the spaces between your toes. Also check your genital area and between your buttocks.

## **Diagnostic Considerations**

Although the typical patient with cutaneous squamous cell carcinoma (cSCC) is of northern European descent and presents with a family history of skin cancer, a personal history of previous skin cancer, and/or an extensive history of sun exposure, a detailed history and physical examination is crucial. In addition, the clinician should be aware of the risk factors for high-risk disease.

Marjolin ulcer appears as a new area of induration, elevation, or ulceration, at the site of a preexisting scar or ulcer. The diagnosis of Marjolin ulcer should be considered in any ulcer that fails to heal with standard therapy.

Pseudoepitheliomatous hyperplasia (PEH) is a histologic finding in keratoacanthoma and SCC, as well as in certain other reactions, such as tattoo reactions. The clinician must determine whether the PEH is associated with cancer. In addition, with lesions containing PEH in patients with a history of lupus, the clinician must differentiate between lesions that are definitely SCC and lesions of hypertrophic lupus that are mimicking SCC or keratoacanthoma.

## Other conditions to be considered

The following conditions should also be considered when evaluating a patient with suspected SCC:

* Cancerous lesions: Sebaceous cell carcinoma and rhabdomyosarcoma
* Congenital tumors: Dermoids, dermolipomas, and episcleral osseous choristoma
* Conjunctival degeneration: Pinguecula and amyloidosis
* Hereditary lesions: Benign hereditary intraepithelial dyskeratosis
* Lymphoid tumors: Lymphoid neoplasia, benign reactive lymphoid hyperplasia, and leukemic infiltrates
* Neuroectodermal tumors: Nevus, primary acquired melanosis, and melanoma
* Papillomas: Human papillomavirus (HPV) ̶ induced [papillomas](https://emedicine.medscape.com/article/1192618-overview)
* Pseudocancerous lesions: Pseudoepitheliomatous hyperplasia and keratoacanthoma
* Vascular lesions: Angioma, lymphangioma, Kaposi sarcoma, and pyogenic granuloma
* Xanthomatous lesions: Juvenile xanthogranuloma and fibrous xanthoma

## **Differential Diagnoses**

* Actinic Keratosis
* Allergic Contact Dermatitis
* Atopic Dermatitis
* Atypical Fibroxanthoma
* Basal Cell Carcinoma
* Benign Skin Lesions
* Bowenoid Papulosis
* Chemical Burns
* Pyoderma Gangrenosum

## 

## **Epidemiology**

Skin cancers are the most frequently diagnosed cancers in the United States. Determining the number of cSCCs is difficult, however, because reporting of these cases to cancer registries is not required. One report estimated that in 2012, the most recent date for which these figures have been determined, there were over 5.4 million nonmelanoma skin cancers in the United States, with more than 3.3 million people treated.In comparison, the American Cancer Society estimated that 2,001,140 new cases of cancer other than BCC and SCC would be diagnosed in 2024. (Cases of carcinoma in situ located at any site except the urinary bladder were also not included in the figure.)

Of nonmelanoma skin cancers, approximately 80% are BCC and 20% are SCC. Thus, cSCC is the second most common skin cancer and one of the most common cancers overall in the United States.

### Rising incidence

Despite increased knowledge and public education regarding the causes of skin cancer and the importance of avoiding prolonged sun exposure, the incidence of cSCC continues to rise worldwide. A study from South Korea looking at skin cancer incidences between 1999 and 2014 found that the incidence of SCC in that country rose steadily in those years, with the average annual percentage change in men and women being 3.3 and 6.8, respectively.In Rochester, Minnesota, the annual age-adjusted incidence rates for SCC per 100,000 women rose from 47 cases from 1984-1986 to 100 cases from 1990-1992; the corresponding rates for men increased from 126 cases to 191 cases per 100,000 population.

Looking at the incidence of cSCC and melanoma in seven mid- to high-latitude populations, specifically those of Finland, Norway, Sweden, Denmark, Scotland, the Netherlands, and Tasmania (Australia), Olsen et al found that between 1989 and 2020 (1989-2018 for Tasmania), the ratio of the incidence of cSCC to melanoma grew. By the most recent time period studied, cSCC had a higher incidence than melanoma did in all seven populations.

The international rise in the incidence of cSCC is likely multifactorial; speculated causes include the following:

* An aging population
* Improved detection
* Increased use of tanning beds
* Environmental factors, such as depletion of the ozone layer.

Additionally, the number of patients on immunosuppressive therapy, used in solid organ transplantation and various rheumatologic and dermatologic conditions, is increasing. As noted previously, solid organ transplant recipients have a markedly elevated risk of SCC formation. Metastasis may also be more common in this group.

### Geography-related demographics

Patients who live closer to the equator tend to present with cSCC at a younger age than do patients who live more distant from it.

In the aforementioned study by Olsen and colleagues, which looked at the populations of Finland, Norway, Sweden, Denmark, Scotland, the Netherlands, and Tasmania (Australia), the investigators found that the ratio of the incidence of cSCC to melanoma increased the closer a population was to the equator.

The highest incidence of cSCC occurs in Australia, where nonmelanoma skin cancer incidences as high as 1.17 per 100, a rate 5 times greater than all other cancers combined, have been reported.The high incidence is likely due to the large numbers of light-skinned people in this region who have had extensive sun exposure.

### Race-related demographics

SCC is the second leading cause of skin cancer in White individuals. Persons of Irish or Scottish ancestry have the highest prevalence in the United States. SCC is relatively uncommon in people of African or Asian descent. However, SCC in Black persons carries a higher mortality rate, perhaps due to delayed diagnosis, because tumors are more likely to occur in sun-protected areas in these individuals, including the scalp and sites of previous injury and scarring.

### Sex- and age-related demographics

SCC occurs in men 2-3 times more frequently than it does in women, most likely as a result of higher cumulative lifetime UV exposure in men. This increased exposure may be due to greater participation by men in occupations that entail more significant exposure to sunlight or to other occupational hazards, such as soot, oils, or tars.

In the previously described study by Olsen et al, which examined the populations of Finland, Norway, Sweden, Denmark, Scotland, the Netherlands, and Tasmania (Australia), men had a higher incidence ratio for cSCC to melanoma than women did, but in most of the populations, women demonstrated a greater increase in the ratio over time. This suggests, according to the investigators, that UVR exposure in women has increased.

The typical age at presentation for SCC is approximately 70 years. This varies widely, however, and in certain high-risk groups (eg, organ transplant recipients, patients with epidermolysis bullosa), SCC often manifests at a much younger age.

**Recommendations:**

* Cutaneous squamous cell cancer (cSCC) that is resected with negative margins and does not display high-risk features can be safely observed postoperatively
* Consider adjuvant radiotherapy for resected SCC that demonstrates perineural invasion, especially multifocal; in cases of extensive perineural invasion or invasion of named nerves, the nerve should be targeted with radiotherapy back to the skull base
* Patients with periparotid nodal disease should be managed by surgical resection with neck dissection, followed by adjuvant radiotherapy
* Concurrent cisplatin-based chemotherapy can be considered in patients with high-risk pathologic features (eg, margin positivity or extracapsular extension) or in patients with unresectable, locally advanced disease
* Intensified adjuvant therapies, such as radiotherapy for intermediate-risk patients and incorporating systemic therapies concurrently with radiotherapy, may benefit certain classes of patients

### 

The following are considered high-risk clinical features:

* Immunosuppression
* Ear as the tumor site
* Horizontal tumor diameter of >20 mm
* Tumor depth >4 mm; >6 mm indicates a very–high-risk tumor
* Tumor extension beyond the dermis into or through subcutaneous fat
* Perineural invasion
* Desmoplastic subtype
* Poorly differentiated tumor status

The presence of any of the above high-risk features in a patient with primary SCC warrants discussion of the patient in a multidisciplinary team (MDT) meeting.

SCC treatment options include the following [81] :

* Surgical excision for high-risk tumors - A clinical peripheral margin of 6 mm or greater is indicated when surgically achievable and clinically appropriate
* Surgical excision for low-risk tumors - A clinical peripheral margin of 4 mm or greater is indicated when surgically achievable and clinically appropriate
* Mohs micrographic surgery should be considered for selected patients with high-risk tumors when tissue preservation or margin control is challenging, as well as for patients with any tumor at a critical anatomic site
* Consider curettage and cautery for patients with low-risk tumors if healthcare professionals have had appropriate training with a blunt curette
* Photodynamic therapy should not be used for treatment of primary SSC
* Consider primary radiotherapy for patients if surgical excision would be extremely challenging or difficult to perform or would be likely to result in an unacceptable functional or aesthetic outcome
* Consider adjuvant radiotherapy for patients with a high risk of local recurrence or with close or involved margins when further surgery carries an increased risk of complications, including functional or aesthetic morbidity

For patients with SCC with any high-risk features, posttreatment follow-up appointments every 3-6 months for 24 months should be offered. Depending on the clinical risk, it may be appropriate to also schedule one 3-year follow-up appointment.

### Dermatological Cooperative Oncology Group

Because data are insufficient regarding the value of regional lymphadenectomy following positive sentinel lymph node biopsy (SLNB), do not perform prophylactic lymphadenectomy.

When lymph node metastasis is clinically manifested, the patient should undergo regional (therapeutic) lymphadenectomy.

When local disease is inoperable or not completely resectable, radiation therapy should be performed.

The following cases should prompt use of postoperative radiation therapy:

* R1 or R2 resection (if reexcision is not feasible)
* Extensive lymph node involvement (>1 affected lymph node, lymph node metastasis >3 cm, capsular penetration)
* Intraparotid lymph node involvement

Existence of the following risk factors should prompt treatment with adjuvant radiation therapy:

* Surgical margins < 2 mm and reexcision is not feasible
* Extensive perineural infiltration

Employ micrographically controlled surgery (MCS) for the treatment of local or locoregional recurrence.

If, over the course of the resection, residual, unresectable tumor tissue (R1 or R2 resection) is in evidence, the affected area should undergo radiation therapy.

If an interdisciplinary tumor board determines inoperability, radiation therapy should be performed.

*Pretreatment for cSCC*

If there is any diagnostic uncertainty, histologic confirmation of cSCC lesions should be obtained before planning definitive treatment.

Before performing any diagnostic or treatment procedure, the following should be recorded:

* Maximum clinical cSCC lesion dimension (typically diameter, in mm)
* The plane of the deep‐excision margin
* Whether the tumor is recurrent or whether it is in a field of previous radiotherapy
* The immunocompetency of the patient

*Treatment options for primary cSCC*

The first-line treatment that should be offered to people with resectable primary cSCC is surgical excision.

Determine peripheral tumor margins under bright lighting with magnification or with dermoscopy.

The following should be offered to patients with cSCC who have one or more involved margins or margins less than 1 mm, in whom patient or tumor factors suggest higher risk:

* Wide local excision (delayed reconstruction likely)
* Mohs micrographic surgery
* Adjuvant radiotherapy

Active treatment can be offered to immunosuppressed cSCC patients who have one or more clear‐but‐close (< 1 mm) or involved margins, followed by structured follow‐up and surveillance.

If patients have symptomatic perineural invasion or radiologic evidence of perineural invasion, their case should be discussed by a specialist skin cancer multidisciplinary team.

Mohs micrographic surgery can also be considered in selected patients with cSCC after discussion by a specialist skin cancer multidisciplinary team; this particularly applies to cases in which tumor margins are difficult to delineate or in locations where tissue conservation is important for function.

Before considering radiotherapy in patients with histologically proven cSCC, discuss the case with a multidisciplinary team—either a local skin cancer multidisciplinary team or a specialist skin cancer multidisciplinary team—with a clinical oncologist present.

Curettage and cautery with curative intent can be considered in immunocompetent patients with low-risk, small (< 1 cm), well‐defined, nonrecurrent cSCC.

*Locally advanced, recurrent, and metastatic cSCC*

In patients with the following variables, an individualized specialist skin cancer multidisciplinary team should be involved to include multimodality and imaging treatment plans:

* Regional lymph node metastasis
* Immunocompromise with locally advanced and/or metastatic cSCC
* In-transit metastases from cSCC
* Metastatic cSCC, with the patient having experienced further locoregional relapse following lymphadenectomy

Therapeutic regional lymphadenectomy should be offered to patients with head and neck cSCC with regional lymph node metastasis. It should also be offered to patients with non–head and neck cSCC who have regional lymph node metastases in axillary, inguinofemoral, or other peripheral draining nodes.

Adjuvant radiotherapy should be offered after therapeutic regional lymphadenectomy to patients with cSCC who have high‐risk pathology.

*Insufficient evidence to support any recommendation for cSCC*

The evidence is insufficient to support any recommendations for the following therapies in the treatment of cSCC:

* Cryotherapy
* Carbon dioxide laser therapy
* Topical therapies

## **Outlook / Prognosis**

Most cases of squamous cell carcinoma have a positive prognosis and an excellent survival rate if you receive an early diagnosis. Early detection and treatment prevent the tumor from growing and damaging other parts of your body.

If your healthcare provider removes your cancer, there’s a chance it can return in the future. Make sure to follow up with your healthcare provider to verify you’re cancer-free. It’s also important to protect your skin from UV rays when outdoors.

**Answers to questions about Squamous Cell Carcinoma (SCC)**

## 1. Do I have skin cancer? What kind?

Yes, you have Squamous Cell Carcinoma (SCC), a common type of skin cancer that arises from the squamous cells in the outer layer of the skin. It often appears as a scaly, crusted, or ulcerated lesion, usually on sun-exposed areas.

## 2. Is this type of cancer likely to spread?

SCC can spread (metastasize), but this is uncommon if caught early. Larger, deeper, or recurrent tumors and those in high-risk locations have a higher chance of spreading to lymph nodes or other parts of the body.

## 3. Has my cancer spread?

Your doctor will use physical exams, imaging, and possibly biopsy of lymph nodes to check for spread. Most early-stage SCCs have not spread. If spread is detected, additional treatments will be needed.

## 4. What treatment do you recommend?

Treatment depends on the tumor size, location, and risk factors:

* Surgery (excisional or Mohs micrographic surgery) is the most common and effective treatment, especially for early-stage SCC.
* Cryosurgery, curettage and electrodesiccation, laser surgery, or photodynamic therapy may be options for small, superficial lesions.
* Radiation therapy can be used if surgery isn't suitable or for advanced cases.
* Topical medications like 5-fluorouracil or imiquimod may be used for superficial SCC.
* For advanced or metastatic SCC, immunotherapy (e.g., cemiplimab) or chemotherapy may be recommended.

## 5. What are the possible side effects of this treatment?

* Surgery: Pain, bleeding, infection, scarring, and possible changes in skin appearance.
* Radiation: Skin redness, irritation, fatigue, and possible long-term skin changes.
* Topical treatments: Local redness, irritation, and inflammation.
* Immunotherapy: Fatigue, rash, diarrhea, and immune-related side effects like inflammation of organs.

## 6. Will I have a scar after treatment?

Yes, most treatments, especially surgery, will leave a scar. Mohs surgery aims to minimize scarring by removing only cancerous tissue. The size and appearance depend on tumor size and location.

## 7. Is this cancer likely to come back?

SCC can recur, particularly if the tumor was large, deep, or in a high-risk location. Regular follow-up is important to detect recurrences early.

## 8. Am I at risk of other types of skin cancer?

Yes, having SCC increases your risk of developing other skin cancers, including basal cell carcinoma and melanoma. Sun protection and regular skin checks are essential.

## 9. What can I do to prevent skin cancer?

* Avoid excessive sun exposure and tanning beds.
* Use broad-spectrum sunscreen daily.
* Wear protective clothing and hats.
* Perform regular self-exams and see a dermatologist annually or as recommended.

## 10. How often will I need follow-up visits after treatment?

Typically, follow-up visits are every 3 to 6 months for the first couple of years, then annually if no recurrence. Your doctor will tailor follow-up based on your risk factors.

## 

## **Genomic Data of Squamous Cell Carcinoma (SCC) of the Skin**

## 1. High Mutation Burden

* SCC tumors have a mutation rate exceeding 50–60 mutations per megabase, with a median of about 1,200 mutations per tumor, which is 5–15 times higher than many other cancers.
* This high mutation load is mainly due to chronic UV exposure causing DNA damage in skin cells.

## 2. Commonly Mutated Genes

* TP53: The most frequently mutated tumor suppressor gene in SCC, involved in DNA repair and apoptosis. Mutations impair the cell’s ability to control damaged DNA, promoting cancer development.
* NOTCH1 and NOTCH2: Mutated in over 75% of SCC cases, these genes regulate cell differentiation and growth; their loss leads to uncontrolled proliferation.
* HRAS: An oncogene mutated in some SCCs, contributing to abnormal cell signaling and growth.
* TERT promoter: Mutations here activate telomerase, enabling cellular immortality (noted in some studies).
* Other frequently mutated genes include EP300, PBRM1, USP28, CHUK, CDKN2A, and genes involved in chromatin remodeling, cell cycle control, and the Ras/MAPK/PI3K pathways.

## 3. Genomic Instability and Chromosomal Alterations

* SCC exhibits chromosomal instability with frequent copy number alterations and polyploidy, contributing to tumor progression.
* UV hotspot mutations in genes like KNSTRN disrupt chromatid cohesion, leading to aneuploidy.

## 4. Mutation Patterns and Tumor Heterogeneity

* SCC tumors show high intra-tumor heterogeneity, with different mutations present in distinct tumor regions.
* Many mutations found in SCC are also present in normal sun-exposed skin, suggesting that accumulation and combination of mutations drive carcinogenesis rather than single mutations alone.

## 5. Differences Between Localized and Metastatic SCC

* Studies show that mutations in TP53, TERT, SPEN, MLL3, and NOTCH2 are more frequent in metastatic SCC compared to localized tumors, indicating their role in aggressive disease.
* Metastatic SCCs also exhibit more nonsense mutations and fewer silent mutations compared to localized SCCs.

## 6. Genetic Syndromes and Hereditary Factors

* Certain inherited syndromes increase SCC risk, such as Fanconi anemia and Basal Cell Nevus Syndrome (Gorlin syndrome), involving mutations in DNA repair and tumor suppressor genes like PTCH1.
* Mutations in CDKN2A and other cell cycle regulators also contribute to genetic susceptibility

**doctor-patient conversation about Squamous Cell Carcinoma (SCC) of the skin**

Doctor:  
“Hello, I’ve reviewed your biopsy results, and you have squamous cell carcinoma, which is a common type of skin cancer that arises from the outer layer of your skin.”

Patient:  
“What exactly is squamous cell carcinoma? Is it dangerous?”

Doctor:  
“SCC starts in the squamous cells that make up most of the skin’s surface. It usually grows slowly and is often curable, especially when detected early. However, if left untreated, it can grow deeper and spread to nearby tissues or lymph nodes, which can be serious.”

Patient:  
“How did I get this? Can it spread to other parts of my body?”

Doctor:  
“The main cause is long-term exposure to ultraviolet (UV) radiation from the sun or tanning beds. Yes, SCC can spread, but this is uncommon if treated early. Larger or more aggressive tumors have a higher risk of spreading.”

Patient:  
“What treatment do you recommend for me?”

Doctor:  
“The best treatment is usually surgical removal of the tumor. We can use Mohs surgery, which removes the cancer layer by layer while preserving healthy tissue, especially for tumors on the face or other sensitive areas. For smaller or superficial lesions, other options like cryotherapy or topical treatments may be considered. If the cancer has spread, additional treatments such as radiation or immunotherapy might be necessary.”

Patient:  
“What are the side effects of treatment? Will I have a scar?”

Doctor:  
“Surgery may cause some pain, redness, and swelling initially, and it will leave a scar. Mohs surgery often results in smaller scars compared to traditional excision. Other treatments have their own side effects, which we will discuss in detail. Most people heal well within a few weeks.”

Patient:  
“Is there a chance the cancer will come back?”

Doctor:  
“Yes, SCC can recur, especially if it was large or in a high-risk area. That’s why regular follow-up visits are important to catch any new or returning cancers early.”

Patient:  
“Am I at risk of other types of skin cancer?”

Doctor:  
“Having SCC increases your risk of developing other skin cancers, including basal cell carcinoma and melanoma. Protecting your skin from the sun and regular skin exams are key to prevention.”

Patient:  
“What can I do to prevent this from happening again?”

Doctor:  
“Avoid excessive sun exposure, use broad-spectrum sunscreen daily, wear protective clothing, and avoid tanning beds. Also, regularly check your skin for any new or changing spots and see your doctor promptly if you notice anything suspicious.”

Patient:  
“How often will I need follow-up visits?”

Doctor:  
“Typically, we recommend skin exams every 3 to 6 months for the first couple of years, then annually if no recurrence is detected. We will tailor this to your individual risk.”

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**SQUAMOUS CELL CARCINOMA (LUNGS)**

**DEFINITION AND DESCRIPTION**

Squamous cell carcinoma of the lung is a type of lung cancer. It occurs when abnormal lung cells multiply out of control and form a tumor. Eventually, tumor cells can spread (metastasize) to other parts of the body including the

* lymph nodes around and between the lungs
* liver
* bones
* adrenal glands
* brain.

In general, there are two categories of lung cancer: small cell lung cancer and non-small cell lung cancer. The cancer cells in each type look different under the microscope. They are also treated differently. The prognosis for non-small cell lung cancer tends to be better than for small cell lung cancer; non-small cell lung cancers are more likely to be contained in one area, making treatment more likely to be successful.

Squamous cell carcinoma is one type of non-small cell lung cancer. The others are:

* adenocarcinoma
* large cell carcinoma.

Adenocarcinoma is the most common type of lung cancer. Squamous cell carcinoma is the second-most common type. It accounts for about 30% of all cases of non-small cell lung cancer.

**RISK FACTORS**

Your risk of all types of lung cancer, including squamous cell carcinoma, increase if you:

* smoke. Smoking cigarettes is by far the leading risk factor for lung cancer. In fact, cigarette smokers are 13 times more likely to develop lung cancer than nonsmokers. Cigar and pipe smoking are almost as likely to cause lung cancer as cigarette smoking.
* breathe tobacco smoke. Nonsmokers who inhale fumes from cigarette, cigar, and pipe smoking have an increased risk of lung cancer.
* are exposed to radon gas. Radon is a colorless, odorless radioactive gas formed in the ground. It seeps into the lower floors of homes and other buildings and can contaminate drinking water. Radon exposure is the second leading cause of lung cancer. It's not clear whether elevated radon levels contribute to lung cancer in nonsmokers. But radon exposure does contribute to lung cancer in smokers and in people who regularly breathe high amounts of the gas at work (miners, for example). You can test radon levels in your home with a radon testing kit.
* are exposed to asbestos. Asbestos is a mineral used in insulation, fireproofing materials, floor and ceiling tiles, automobile brake linings, and other products. People exposed to asbestos on the job (miners, construction workers, shipyard workers, and some auto mechanics) have a higher-than-normal risk of lung cancer. People who live or work in buildings with asbestos-containing materials that are deteriorating also have an increased risk of lung cancer. The risk is even higher in people who also smoke. Asbestos exposure also increases the risk of developing mesothelioma. It's a relatively rare and usually fatal cancer that starts in the lining of the lungs.
* are exposed to other cancer-causing agents at work. These include uranium, arsenic, vinyl chloride, nickel chromates, coal products, mustard gas, chloromethyl ethers, gasoline, and diesel exhaust.

Most cases of squamous cell carcinoma start in the center of the lungs. These tumors may cause some symptoms, such as coughing up blood, at an earlier stage than tumors on the edges of the lungs, such as adenocarcinomas.

Squamous cell carcinoma often spreads (metastasizes) to other parts of the body because of the constant flow of fluids (blood and lymph) through the lungs. The fluids can carry cancer cells to nearby areas, such as the chest wall, neck, esophagus, and the protective sac around the heart. Unless it is diagnosed and treated early, it often spreads throughout the body.

Some lung cancers have the ability to secrete chemicals that circulate in the bloodstream. These chemicals can change the way the body functions. Squamous cell lung cancer may secrete a substance that leads to abnormally high blood calcium levels. This can cause dehydration, constipation, kidney problems and confusion.

## **Symptoms**

Early on, squamous cell lung cancer may have no symptoms. If symptoms occur, they may include:

* a cough that doesn't go away
* coughing up blood or mucus
* shortness of breath or trouble breathing
* wheezing
* fatigue
* discomfort when swallowing
* chest pain
* fever
* hoarseness
* unexplained weight loss
* poor appetite
* high levels of calcium in the blood.

If the cancer has spread beyond the lungs, it can cause other symptoms. For example, you may have bone pain if it has spread to your bones, or headaches and seizures if it has spread to your brain.

Many of these symptoms can be caused by other conditions. See your doctor if you have symptoms so that the problem can be diagnosed and properly treated.

## **Diagnosis**

Your doctor may suspect lung cancer based on:

* your symptoms
* your smoking history
* whether you live with a smoker
* your exposure to asbestos and other cancer-causing agents.

To look for evidence of cancer, your doctor will examine you, paying special attention to your throat, neck, lymph nodes and lungs. He or she will order imaging tests to check your lungs for masses. In most cases, a chest x-ray will be done first. If the x-ray shows anything suspicious, a CT scan will be done. As the scanner moves around you, it takes many pictures. A computer then combines the images. This creates a more detailed image of the lungs, allowing doctors to confirm the size and location of a mass or tumor.

You may also have a magnetic resonance imaging (MRI) scan or a positron emission tomography (PET) scan. MRI scans provide detailed pictures of the body's organs, but they use radio waves and magnets to create the images, not x-rays. PET scans look at the function of tissue rather than anatomy. Lung cancer tends to show intense metabolic activity on a PET scan. Some medical centers offer combined PET-CT scanning.

If cancer is suspected based on these images, more tests will be done to make the diagnosis, determine the type of cancer, and see if it has spread. These tests may include the following:

* Sputum sample. Coughed-up mucus is checked for cancer cells.
* Biopsy. A sample of abnormal lung tissue is removed and examined under a microscope in a laboratory. If the tissue contains cancer cells, the type of cancer can be determined by the way the cells look under the microscope. The tissue is often obtained during a bronchoscopy. However, surgery may be necessary to expose the suspicious area.
* Bronchoscopy. During this procedure, a tube-like instrument is passed down the throat and into the lungs. A camera on the end of the tube allows doctors to look for cancer. Doctors can remove a small piece of tissue for a biopsy.
* Mediastinoscopy. In this procedure, a tube-like instrument is used to biopsy lymph nodes or masses between the lungs. (This area is called the mediastinum.) A biopsy obtained this way can diagnose the type of lung cancer and determine whether the cancer has spread to lymph nodes.
* Fine-needle aspiration. With a CT scan, a suspicious area can be identified. A tiny needle is then inserted into that part of the lung or pleura. The needle removes a bit of tissue for examination in a laboratory. The type of cancer can then be diagnosed.
* Thoracentesis. If there is fluid build-up in the chest, it can be drained with a sterile needle. The fluid is then checked for cancer cells.
* Video-assisted thoracoscopic surgery (VATS). In this procedure, a surgeon inserts a flexible tube with a video camera on the end into the chest through an incision. He or she can then look for cancer in the space between the lungs and the chest wall and on the edge of the lung. Abnormal lung tissue can also be removed for a biopsy.
* Additional imaging tests to look for cancer spread. These imaging tests can detect lung cancer that has spread to the bones, brain, or other parts of the body.

Occasionally, surgery is done to remove the tumor first; the diagnosis is made after the tumor has been examined in a laboratory.

After the cancer has been diagnosed, it is assigned a "stage." The stages of squamous cell carcinoma reflect the tumor's size and how far the cancer has spread. Stages I through III are further divided into A and B categories.

* Stage I tumors are small and have not invaded the surrounding tissue or organs.
* Stage II and III tumors have invaded surrounding tissue and/or organs and have spread to lymph nodes.
* Stage IV tumors have spread beyond the chest.

## **Expected duration**

Squamous cell lung cancer will continue to grow until it is treated. As with any cancer, even if it seems to be cured after treatment, this lung cancer can return.

## **Prevention**

To reduce your risk of squamous cell lung cancer:

* Don't smoke. If you already smoke, talk to your doctor about getting the help you need to quit.
* Avoid secondhand smoke. Choose smoke-free restaurants and hotels. Ask guests to smoke outdoors, especially if there are children in your home.
* Reduce exposure to radon. Have your home checked for radon gas. A radon level above 4 picocuries/liter is unsafe. If you have a private well, have your drinking water checked, too. Kits to test for radon are widely available.
* Reduce exposure to asbestos. Because there is no safe level of asbestos exposure, any exposure is too much. If you have an older home, check to see if any insulation or other asbestos-containing material is exposed or deteriorating. The asbestos in these areas must be professionally removed or sealed up. If the removal isn't done properly, you may be exposed to more asbestos than you would have been if it had been left alone. People who work with asbestos-containing materials should use approved measures to limit their exposure and to prevent bringing asbestos dust home on their clothing.

Annual screening for lung cancer with low-dose computed tomography in adults ages 50 to 80 years if you:

* Have a 20 pack-year smoking history (pack years is calculated by multiplying the number of cigarettes smoked per day times the number of years you smoked), AND
* Currently smoke or have quit within the past 15 years, AND
* Are healthy enough to undergo lung cancer surgery.

The decision to proceed with lung cancer screening is not straightforward. Many so-called abnormalities found on CT scans are not cancerous. However patients will often undergo extensive testing, including surgery, to find out. CT scan screening is an individualized decision to be made with your doctor.

## **Treatment**

Treatment depends on the cancer's stage as well as the patient's condition, lung function, and other factors. (Some patients may have other lung conditions, such as emphysema or COPD—chronic obstructive pulmonary disease.) If the cancer has not spread, surgery is usually the treatment of choice. There are three types of surgery:

* Wedge resection removes only a small part of the lung
* Lobectomy removes one lobe of the lung
* Pneumonectomy removes an entire lung.

Lymph nodes are also removed and examined to see if the cancer has spread.

Some surgeons use video-assisted thoracoscopy (VATS) to remove small, early-stage tumors, especially if the tumors are near the outer edge of the lung. (VATS can also be used to diagnose lung cancer.) Because the incisions for VATS are small, this technique is less invasive than a traditional "open" procedure.

Because surgery will remove part or all of a lung, breathing may be more difficult afterwards, especially in patients with other lung conditions (emphysema, for example). Doctors can test lung function prior to surgery and predict how it might be affected by surgery.

Depending on how far the cancer has spread, treatment may include chemotherapy (the use of anticancer drugs) and radiation therapy. These may be given before and/or after surgery. Unfortunately, squamous cell carcinoma does not respond to chemotherapy and radiation therapy as well as other types of tumors.

When the tumor has spread significantly, chemotherapy and/or immunotherapy may be recommended to slow its growth, even if it cannot cure the disease. These therapies have been shown to ease symptoms and prolong life in cases of advanced lung cancer. Radiation therapy can relieve symptoms, too. It is often used to treat lung cancer that has spread to the brain or bones and is causing pain. It can also be used alone or with chemotherapy to treat lung cancer that is confined to the chest.

People who may not withstand surgery due to other serious medical problems may receive radiation therapy, with or without chemotherapy, to shrink the tumor.

Cancerous tissue may be tested for specific genetic abnormalities (mutations). Doctors may then be able to treat the cancer with a "targeted therapy." These therapies can derail the cancer's growth by preventing or changing chemical reactions linked to particular mutations. For example, some target therapies prevent cancer cells from receiving chemical "messages" telling them to grow. However, these specific mutations tend to occur less frequently in squamous cell cancers compared to adenocarcinomas.

Knowing about specific genetic mutations can help predict which therapy will be best. This strategy can be especially helpful in certain patients, such as women with adenocarcinoma of the lung who have never smoked.

Even after treatment has been completed, lung cancer patients must return for regular follow-up appointments. Even if the cancer was initially placed into remission," it can return months or even years later.

## **When to call a professional**

If you have any symptoms of squamous cell lung cancer, see your doctor as soon as possible.

## **Prognosis**

Squamous cell lung cancer usually is diagnosed after the disease has spread, so the prognosis is often guarded. The survival rate is significantly higher if the disease is detected and treated early.

Even when surgery and other therapies are initially successful, squamous cell lung cancer can return. This is because cancer cells can start to spread without being detected right away.

**Targeted Therapy**

For advanced cancers, treatment should be tailored according to genetic and molecular testing, including *ALK* rearrangement, *ROS1* fusion, *EGFR, BRAF, NTRK* 1/2/3, *MET* exon 14 skipping, *RET* rearrangement, Her2 mutations, and PD-L1 testing.

* **PD-L1 ≥50%:** In patients with advanced SCC of the lung with PD-L1 ≥50%, preferred options for first-line treatment include single-agent pembrolizumab, cemiplimab, or atezolizumab, the combination of carboplatin with paclitaxel or albumin-bound paclitaxel and pembrolizumab, or cemiplimab with chemotherapy.
* **PD-L1 1% to 49%**: For SCC of the lung in this category, preferred first-line treatment options include combination chemotherapy with either pembrolizumab or cemiplimab.
* ***EGFR* exon 19 deletion or exon 21 L858R mutations**: Osimertinib is the preferred agent. At progression there, patients can be treated with doublet chemotherapy and immune checkpoint inhibitor therapy. Patients treated with either erlotinib, afatinib, gefitinib, or dacomitinib in the first-line setting can be switched to osimertinib at progression after confirming T790M mutation either on liquid biopsy or tumor sample.
* ***EGFR* S768I, L861Q, or G719X mutations**: Preferred agents for these groups of patients include afatinib or osimertinib.
* ***KRAS*** **G12C**: These patients are initially treated based on PD-L1 status and, at progression, are treated with either sotorasib or adagrasib.
* ***ALK* rearrangement**: When *ALK* rearrangement is detected before the initiation of any systemic therapy for advanced SCC of the lung, it is preferred to use TKI therapy using agents alectinib, brigatinib, or lorlatinib.
* ***ROS1*** **rearrangement**: Patients with advanced ROS1 rearrangement cancers can be treated in a first-line setting with TKI therapies, including entrectinib, crizotinib, or repotrectinib.
* ***BRAF* V600E mutation**: In patients with *BRAF* V600E mutation that is identified before any systemic therapies, it is preferred to BRAF/MEK inhibitor therapy, including either a combination of dabrafenib and trametinib or encorafenib and binimetinib.
* ***NTRK* 1/2/3 fusion**: Larotrectinib or entrectinib can be used first-line to treat advanced SCC of the lung harboring *NTRK* gene fusion.
* ***MET* exon 14 skipping mutation**: Advanced NSCLC patients with *MET* exon 14 skip mutation now have the option of first-line targeted therapy with capmatinib or tepotinib.
* ***RET* rearrangement**: Preferred first-line targeted therapies of either selpercatinib or pralsetinib are currently available for NSCLC harboring *RET* rearrangements.
* **Her2 mutation**: For patients with NSCLC in advanced stages harboring her2 mutations, trastuzumab deruxtecan is currently approved for second-line use after progression on first-line systemic chemotherapy to chemoimmunotherapy.

**EPIDEMIOLOGY**

In 2023, lung cancer was the third most common cancer in terms of incidence and the most common cause of cancer-related mortality in the US, as per the National Cancer Institute's Surveillance Epidemiology and End Results (NCI SEER) database. Lung cancer incidence was estimated at 238,340 cases, accounting for 12% of the cancer burden in the US. The estimated mortality for lung cancer in 2023 was 127,070 deaths, constituting around 21% of all US cancer-related deaths. Approximately 85% of all lung cancers are NSCLCs. Adenocarcinoma and squamous cell carcinoma are the most common subtypes, accounting for 50% and 30% of NSCLC cases, respectively.

## **Common Questions and Answers**

1. What is squamous cell carcinoma of the lung?  
Squamous cell carcinoma (SCC) of the lung is a subtype of non-small cell lung cancer (NSCLC) that originates in the flat, thin squamous cells lining the airways. It accounts for about 25–30% of lung cancers and typically arises in the central bronchi (large airways).

2. What causes lung squamous cell carcinoma?  
The primary cause is cigarette smoking. Other risk factors include exposure to secondhand smoke, asbestos, radon, occupational carcinogens, prior radiation or chemotherapy, and HIV infection.

3. What are the symptoms of lung SCC?  
Symptoms often appear in later stages and include:

* Persistent cough (sometimes with blood)
* Chest pain
* Shortness of breath
* Hoarseness
* Wheezing
* Recurrent chest infections
* Fatigue, loss of appetite, and weight loss.

4. How is lung SCC diagnosed?  
Diagnosis involves physical examination, imaging tests (CT, PET scans), biopsy via bronchoscopy or needle aspiration, and laboratory tests. Sometimes sputum cytology or fluid sampling (thoracentesis) is used.

5. What are the stages of lung SCC?

* Stage 0: Cancer confined to the top layer of airway lining
* Stage 1: Tumor grows deeper but no lymph node involvement
* Stage 2: Involvement of nearby lymph nodes but no distant spread
* Stage 3: Spread to multiple lymph nodes or nearby chest organs
* Stage 4: Distant metastasis to other organs or lymph nodes.

6. What treatment options are available?  
Treatment depends on stage and patient health:

* Surgery for early stages
* Chemotherapy and radiation therapy for locally advanced or inoperable tumors
* Immunotherapy (e.g., pembrolizumab) combined with chemotherapy for advanced disease
* Targeted therapies are less common but may be used in select cases.

7. What are the side effects of treatments?

* Surgery: Pain, fatigue, infection risk, reduced lung function
* Chemotherapy: Nausea, vomiting, hair loss, fatigue, low blood counts, neuropathy
* Radiation: Skin irritation, cough, fatigue, pneumonitis
* Immunotherapy: Fatigue, rash, diarrhea, immune-related inflammation of organs.

8. Can lung SCC be cured?  
Early-stage lung SCC can potentially be cured with surgery and adjuvant therapies. Advanced stages focus on control and symptom relief. Prognosis depends on stage at diagnosis and overall health.

9. How can I reduce my risk of lung SCC?

* Avoid smoking and exposure to secondhand smoke
* Limit exposure to occupational carcinogens and radon
* Maintain a healthy lifestyle and get regular medical check-ups.

**Doctor-patient conversation about Squamous Cell Carcinoma (SCC) of the Lung**

Doctor:  
“Hello, I have your test results, and you have squamous cell carcinoma of the lung. This is a type of non-small cell lung cancer that arises from the squamous cells lining your airways.”

Patient:  
“What exactly does that mean? How serious is it?”

Doctor:  
“Squamous cell lung cancer is often linked to smoking and usually develops in the central parts of the lungs. The seriousness depends on the stage — how large the tumor is and whether it has spread. We will use scans and biopsies to determine this.”

Patient:  
“Has the cancer spread beyond my lungs?”

Doctor:  
“We are doing imaging tests like CT and PET scans to check for spread to lymph nodes or other organs. This information helps us decide the best treatment.”

Patient:  
“What treatment options do I have?”

Doctor:  
“If the cancer is caught early and localized, surgery to remove the tumor or part of the lung is often the best option. For more advanced cases, chemotherapy and radiation therapy are used. Recently, immunotherapy drugs like pembrolizumab have improved outcomes, especially in advanced disease. Sometimes these treatments are combined.”

Patient:  
“What are the side effects of these treatments?”

Doctor:  
“Surgery can cause pain, fatigue, and breathing difficulties initially. Chemotherapy may cause nausea, hair loss, fatigue, and low blood counts. Radiation can cause skin irritation and cough. Immunotherapy can cause fatigue, rash, and inflammation of organs, but many patients tolerate it well.”

Patient:  
“How long will treatment last? Will I be able to work?”

Doctor:  
“Treatment length varies. Surgery recovery may take weeks, chemotherapy cycles typically last a few months, and immunotherapy may continue longer. Many patients can continue some daily activities, but fatigue and other side effects may require adjustments.”

Patient:  
“What is the goal of treatment?”

Doctor:  
“For early-stage cancer, the goal is cure. For advanced cancer, we aim to control the disease, relieve symptoms, and improve quality of life.”

Patient:  
“Should I get a second opinion?”

Doctor:  
“It’s always a good idea to seek a second opinion, especially for complex cases. I can recommend specialists experienced in lung cancer.”

Patient:  
“How often will I need follow-up?”

Doctor:  
“After treatment, we will schedule regular scans and visits every few months initially, then less frequently if you remain stable.”

## 

## **Differential Diagnosis of Squamous Cell Carcinoma (SCC) of the Lung**

## 1. Non-Malignant Diseases with Similar Symptoms

SCC symptoms such as chronic cough, weight loss, hemoptysis, and dyspnea overlap with:

* Pulmonary tuberculosis
* Sarcoidosis
* Pneumonia
* Pulmonary fungal infections
* Other chronic inflammatory lung diseases  
  These conditions must be ruled out through clinical, microbiological, and imaging studies.

## 2. Other Lung Cancers

* Adenocarcinoma (solid pattern):
  + Lacks squamous markers (p40, p63) on immunohistochemistry (IHC).
  + Important to differentiate as treatment differs.
* Small Cell Lung Carcinoma (SCLC):
  + Shows neuroendocrine markers and TTF1 positivity.
  + Typically more aggressive with different chemotherapy protocols.
* Large Cell Carcinoma and Large Cell Neuroendocrine Carcinoma:
  + May have overlapping features but differ in morphology and immunoprofile.
* Adenosquamous Carcinoma:
  + Contains both adenocarcinoma and squamous components (>10%).
  + Molecular testing is important for treatment decisions.
* Pleomorphic (Sarcomatoid) Carcinoma:
  + Contains spindle or giant cells mixed with SCC elements.

## 3. Metastatic Tumors to the Lung

* Pulmonary metastasis from head and neck squamous cell carcinoma (HNSCC):
  + Clinically important to differentiate from primary lung SCC as treatment and prognosis differ.
  + Diagnosis involves combined clinical, pathological, immunohistochemical, and molecular analyses.
* Other metastases: From melanoma, breast, or other primaries may mimic SCC histologically.

## 4. Rare and Specific Tumor Types

* NUT Carcinoma:
  + Aggressive carcinoma positive for NUT protein by IHC or FISH/NGS testing.
* Lymphoepithelial Carcinoma:
  + Poorly differentiated SCC with prominent lymphoid infiltrate, often EBV positive.
* Mucoepidermoid Carcinoma:
  + Contains mucocytes, lacks keratinization typical of SCC.

## 5. Squamous Cell Metaplasia

* Reactive squamous cell changes due to lung injury without a mass lesion.
* Does not form a tumor and lacks malignant features

REFERENCES

[Squamous Cell Carcinoma of the Lung - Harvard Health](https://www.health.harvard.edu/cancer/squamous-cell-carcinoma-of-the-lung-a-to-z)

[Squamous Cell Lung Cancer - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK564510/#article-29417.s10)

## 

## **squamous cell skin cancer of the head and neck**

Skin malignancies are the most common cancer in the United States, responsible for more than half of all new cancer cases. These can be broken down into melanoma and non-melanoma malignancies, which are squamous cell cancer and basal cell cancer. These skin malignancies are caused by ultraviolet radiation from exposure to the sun and tanning beds.

Squamous cell cancer is the second most common form of skin cancer. It is more aggressive and may require extensive surgery depending on location and nerve involvement. Radiation, chemotherapy and immunotherapy are used in advanced cases.

## **Symptoms of squamous cell skin cancer of the head and neck**

Squamous cell skin cancers usually present as an abnormal growth on the skin or lip. The growth may have the appearance of a wart, crusty spot, ulcer, mole or a sore that does not heal. It may or may not bleed and can be painful. If you have a preexisting mole, any changes in the characteristics of this spot — such as a raised or irregular border, irregular shape, change in color, increase in size, itching or bleeding — are warning signs. Pain and nerve weakness are concerning for cancer that has spread. Sometimes a lump in the neck can be the only presenting sign of skin cancer that has spread to lymph nodes, particularly when there is a history of previous skin lesion removal.

## **Risk factors for squamous cell skin cancer of the head and neck**

* Sun exposure.
* Tanning bed exposure.
* Fair skin.
* Age over 50 years.
* A history of skin cancer or precancerous skin lesions.
* A previous burn.
* Prior radiation to the head and neck area.
* Immunosuppression, either from a medical condition or by medications (such as those taken by transplant patients).
* Certain sun-sensitive conditions such as xeroderma pigmentosum.

## **Diagnosis**

Diagnosis is made by clinical exam and a biopsy. Squamous cell cancers are staged by size and extent of growth. Squamous cell cancers can metastasize to nearby lymph nodes or other organs, and can invade both small and large nerves and local structures.

Biopsy can help determine if the squamous cell cancer is a low-risk tumor or a high-risk tumor that requires more aggressive treatment. Low-risk tumors are less than 10 millimeters in size, less than or equal to 5 millimeters deep and do not involve structures beyond the surrounding fat. High-risk tumors in the head and neck are those that involve the central face, nose and eye area, as well as those tumors that are greater than or equal to 10 millimeters on the cheeks, scalp and neck, tumors that are more than 5 millimeters thick or involve adjacent structures, tumors that invade nerves, tumors that are recurrent or arising from previously radiated tissue, and tumors arising in patients who are immunosuppressed.

## **Treatment**

Surgery is the preferred management method for the majority of squamous cell skin cancers. Low-risk, early stage, small squamous cell cancers can be removed by Mohs surgery, which is a technique that spares normal tissue through repeated intraoperative margin testing, removing only the cancer and leaving adjacent normal tissue. Excision, curettage and desiccation, and cryosurgery can also be used to remove the cancer while sparing normal tissue. Radiation alone is an alternative for low-risk tumors when surgery is not desirable because of cosmetic concerns or medical reasons.

Large tumors and tumors with nerve or lymph node involvement are not suitable for Mohs surgery and require removal of at least 5-millimeter margins of normal tissue around the cancer and neck dissection for involved lymph nodes. Larger tumors require reconstruction, which can be done at the time of surgery if margin status is clear. Reconstruction should be staged when margins status is not clear.

Patients with high-risk tumors should meet with a radiation therapist to discuss postoperative radiation. Chemotherapy may be added to radiation for extensive lymph node involvement or positive margins that cannot be cleared with additional surgery. In patients with high-risk tumors who are not surgical candidates, systemic treatment with both radiation and chemotherapy is used. Such cases require multidisciplinary care by a team of surgeons, radiation oncologists and medical oncologists.

### Generalized treatment recommendations for oral cavity, pharyngeal, and laryngeal cancers

Surgery is preferred for most patients with early or localized disease, and may be considered for locally advanced disease. Selected patients with advanced or metastatic disease may receive surgical resection of their primary tumors, depending on their response to first-line therapy. However, surgery at the primary disease site has a very limited role, if any, in nasopharyngeal cancers, due to their anatomical location and radiosensitivity.

Treatment plans for all disease stages should be discussed at a multidisciplinary tumor conference involving ENT surgeons, radiation oncologists, and medical oncologists. In addition, the following subspecialities and supportive care services should be included in the management for all disease stages:

* Dentistry
* Diagnostic and interventional radiology
* Plastic surgery
* Lymphedema therapy
* Speech/swallowing therapy
* Social work
* Nutrition
* Financial counselors
* Palliative care

Surgery or radiation therapy for early or localized disease (oral cavity, pharyngeal, and laryngeal cancers)

*Stages I-II:*

* Primary treatment for oropharyngeal cancers is surgical resection or definitive radiation therapy.
* Surgery is the preferred approach except for some patients who may have early-stage lip, retromolar trigone, and soft palate cancers.
* Radiation therapy is preferred for patients who may not be able to tolerate surgery.
* The radiation dose depends on tumor size; however, for early-stage disease, doses of 66-72 Gy may be used with adequate results.

### Chemotherapy with radiation therapy for locally advanced disease (oral cavity, pharyngeal, and laryngeal cancers)

*Stages III-IVB*

* Surgery should be considered for locally advanced disease; however, definitive radiation therapy, concurrent chemoradiation alone or after surgery, and induction therapy followed by concurrent chemoradation are alternative options for patients who are not candidates for surgery alone.
* Concurrent chemoradiation therapy is the current standard of care for patients with locally advanced squamous cell carcinoma of the head and neck.
* Chemotherapy is given for the duration of radiation therapy unless otherwise stated; definitive radiation doses used are 66-72 Gy (2.0 Gy/fraction; daily Monday-Friday in 7wk).
* Conventional fractionation for concurrent chemoradiation is up to 72 Gy (2.0 Gy/fraction).
* Postoperative radiation dose is 60-66 Gy (2.0 Gy/fraction); preferred interval between resection and postoperative radiation therapy is ≤ 6wk.
* The decision to treat the patient with concurrent chemoradiation therapy rather than surgery, radiation, or chemotherapy individually should be made by a multidisciplinary tumor board (including a medical oncologist, a radiation therapist, and an ENT surgeon).

*Acceptable chemotherapy regimens for primary systemic therapy with concurrent radiation:*

* Cisplatin 100 mg/m2 IV on days 1, 22, and 43 or 40 mg/m2 IV weekly for 6-7wk or
* Cetuximab 400 mg/m2 IV loading dose 1wk before the start of radiation therapy, then 250 mg/m2 weekly (premedicate with dexamethasone, diphenhydramine, and ranitidine) or
* Cisplatin 20 mg/m2 IV on day 2 weekly for up to 7wk plus paclitaxel 30 mg/m2 IV on day 1 weekly for up to 7wk or
* Cisplatin 20 mg/m2/day IV on days 1-4 and 22-25 plus fluorouracil (5-FU) 1000 mg/m2/day by continuous IV infusion on days 1-4 and 22-25 or
* 5-FU 800 mg/m2 by continuous IV infusion on days 1-5 given on the days of radiation plus hydroxyurea 1 g PO q12h (11 doses per cycle); chemotherapy and radiation given every other week for a total of 13wk or
* Carboplatin 70 mg/m2/day IV on days 1-4, 22-25, and 43-46 plus 5-FU 600 mg/m2/day by continuous IV infusion on days 1-4, 22-25, and 43-46 or
* Carboplatin AUC 1.5 IV on day 1 weekly plus paclitaxel 45 mg/m2 IV on day 1 weekly(see also the Carboplatin AUC Dose Calculation [Calvert formula] calculator)

*Acceptable chemotherapy regimens for patients receiving postoperative concurrent chemoradiation:*

* Cisplatin 100 mg/m2 IV on days 1, 22, and 43 or 40 mg/m2 IV weekly for 6-7wk

### Induction chemotherapy for locally advanced disease (oral cavity, pharyngeal, and laryngeal cancers)

*Stages III-IVB:*

* Induction chemotherapy is typically given to patients with stage III-IVB disease in order to shrink a primary tumor to reduce its bulkiness in preparation for subsequent surgery or radiation therapy.
* The decision to treat with induction chemotherapy rather than concurrent chemoradiation or surgery, radiation, or chemotherapy alone should be made by a multidisciplinary tumor board (including a medical oncologist, a radiation therapist, and an ENT surgeon).

*Acceptable chemotherapy regimens for induction chemotherapy:*

* Docetaxel 75 mg/m2 IV on day 1 plus cisplatin 100 mg/m2 IV on day 1 plus 5-FU 1000 mg/m2/day by continuous IV infusion on days 1-4 every 3wk for three cycles; then 3-8wk later, carboplatin AUC 1.5 IV weekly for up to 7wk during radiation therapy; then 6-12 wk later; pursue surgery if applicable or
* Docetaxel 75 mg/m2 IV on day 1 plus cisplatin 75 mg/m2 IV on day 1 plus 5-FU 750 mg/m2/day by continuous IV infusion on days 1-4 every 3wk for 4 cycles; then 4-7wk later, radiation; surgical resection can be pursued before or after chemotherapy
* Paclitaxel 175 mg/m2 IV on day 1 plus cisplatin 100 mg/m2 IV on day 2 plus 5-FU 500 mg/m2/day by continuous IV infusion on days 2-6 every 3wk for three cycles; then radiation with cisplatin 100 mg/m2 IV on days 1, 22, and 43
* Induction chemotherapy can be followed by concurrent chemoradiation with weekly carboplatin, weekly cisplatin, or weekly cetuximab

### First-line chemotherapy for metastatic or recurrent disease (oral cavity, pharyngeal, and laryngeal cancers)

*Stage IVC:*

* Treatment recommendations include the use of single-agent or combination chemotherapy.
* Platinum-based chemotherapy regimens are preferred if these agents can be tolerated by the patient; if they cannot be tolerated, single agents have been used in this setting.
* Below are first-line chemotherapy options for metastatic disease or recurrent squamous head and neck cancers (after surgery and/or radiation).

*Acceptable chemotherapy regimens in patients with metastatic (incurable) head and neck cancers include (unless otherwise stated, goal is to complete at least six cycles):*

* Cisplatin 100 mg/m2 IV on day 1 every 3wk for six cycles plus 5-FU 1000 mg/m2/day by continuous IV infusion on days 1-4 every 3wk for six cycles plus cetuximab 400 mg/m2 IV loading dose on day 1, then 250 mg/m2 IV weekly until disease progression (premedicate with dexamethasone, diphenhydramine, and ranitidine); or
* Carboplatin AUC 5 IV on day 1 every 3wk for six cycles plus 5-FU 1000 mg/m2/day by continuous IV infusion on days 1-4 every 3wk for six cycles plus cetuximab 400 mg/m2 IV loading dose on day 1, then 250 mg/m2 IV weekly until disease progression (premedicate with dexamethasone, diphenhydramine, and ranitidine); or
* Cisplatin 75 mg/m2 IV on day 1 plus docetaxel 75 mg/m2 IV on day 1 every 3wk or
* Cisplatin 75 mg/m2 IV on day 1 plus paclitaxel 175 mg/m2 IV on day 1 every 3wk or
* Carboplatin AUC 6 IV on day 1 plus docetaxel 65 mg/m2 IV on day 1 every 3wk or
* Carboplatin AUC 6 IV on day 1 plus paclitaxel 200 mg/m2 IV on day 1 every 3wk or
* Cisplatin 75-100 mg/m2 IV on day 1 every 3-4wk plus cetuximab 400 mg/m2 IV loading dose on day 1, then 250 mg/m2 IV weekly or
* Cisplatin 100 mg/m2 IV on day 1 plus 5-FU 1000 mg/m2/day by continuous IV infusion on days 1-4 every 3wk or
* Methotrexate 40 mg/m2 IV weekly (3wk equals one cycle) or
* Paclitaxel 200 mg/m2 IV every 3wk or
* Docetaxel 75 mg/m2 IV every 3wk or
* Cetuximab 400 mg/m2 IV loading dose on day 1, then 250 mg/m2 IV weekly until disease progression or
* Platinum doublet therapy with docetaxel or paclitaxel can be combined with weekly cetuximab for a three-drug regimen option
* Pembrolizumab 200 mg IV every 3wk or 400 mg IV q6wk until disease progression, unacceptable toxicity, or up to 24 months as monotherapy for PD-L1–positive tumors or
* Pembrolizumab 200 mg IV q3wk or 400 mg IV q6wk plus platinum (cisplatin 100 mg/m2 or carboplatin AUC 5) on day 1 plus 5-FU 1000 mg/m2/day by continuous IV infusion on days 1-4 every 3wk

### Second- and third-line chemotherapy for metastatic or recurrent disease (oral cavity, pharyngeal, and laryngeal cancers)

*Stage IVC:*

* Second-line chemotherapy is given after disease progression or recurrence following completion of first-line therapy.
* Third-line therapies are given after disease progression or recurrence following completion of first-line and second-line therapies.
* Second- and third-line regimens are similar to regimens used as first-line therapy but usually offer lower response rates and survival benefits.
* Patients should be treated with platinum-based chemotherapy regimens if they have not previously received a platinum-based drug.

*Acceptable chemotherapy regimens in patients with recurrent head and neck cancers (unless otherwise stated, goal is to complete at least six cycles):*

* Cisplatin 100 mg/m2 IV on day 1 every 3wk for six cycles plus 5-FU 1000 mg/m2/day by continuous IV infusion on days 1-4 every 3wk for 6 cycles plus cetuximab 400 mg/m2 IV loading dose on day 1, then 250 mg/m2 IV weekly until disease progression or
* Carboplatin AUC 5 IV on day 1 every 3wk for six cycles plus 5-FU 1000 mg/m2/day by continuous IV infusion on days 1-4 every 3wk for six cycles plus cetuximab 400 mg/m2 IV loading dose on day 1, then 250 mg/m2 IV weekly until disease progression or
* Cisplatin 75 mg/m2 IV on day 1 plus docetaxel 75 mg/m2 IV on day 1 every 3wk or
* Cisplatin 75 mg/m2 IV on day 1 plus paclitaxel 175 mg/m2 IV on day 1 every 3wk or
* Carboplatin AUC 6 IV on day 1 plus docetaxel 65 mg/m2 IV on day 1 every 3wk or
* Carboplatin AUC 6 IV on day 1 plus paclitaxel 200 mg/m2 IV on day 1 every 3wk or
* Cisplatin 75-100 mg/m2 IV on day 1 every 3-4wk plus cetuximab 400 mg/m2 IV loading dose on day 1, then 250 mg/m2 IV weekly or
* Cisplatin 100 mg/m2 IV on day 1 plus 5-FU 1000 mg/m2/day by continuous IV infusion on days 1-4 every 3wk or
* Methotrexate 40 mg/m2 IV weekly (3wk equals one cycle)or
* Paclitaxel 200 mg/m2 IV every 3wk or
* Docetaxel 75 mg/m2 IV every 3wk or
* Cetuximab 400 mg/m2 IV loading dose on day 1, then 250 mg/m2 IV weekly until disease progression or
* Platinum doublet therapy with docetaxel or paclitaxel can be combined with weekly cetuximab for a three drug regimen option or
* Capecitabine 1250 mg/m2 PO BID days 1–14, then off 7 days (3-week period is one cycle) or
* Afatinib 40 mg PO daily until disease progression or
* Nivolumab 240 mg IV q2wk or 480 mg q4wk until disease progression or
* Pembrolizumab 200 mg IV q3wk or 400 mg IV q6wk until disease progression

### Radiation therapy for early or localized disease (nasopharyngeal cancers)

*Stage I:*

* Patients with early or localized disease may be treated with definitive radiation therapy to the nasopharynx alone
* Radiation doses of 66-72 Gy

### Chemotherapy with radiation therapy for locally advanced nasopharyngeal cancers

*Stages II-IVB:*

* Patients with stage II-IVB nasopharyngeal cancers are treated with concurrent chemotherapy and radiation +/- adjuvant chemotherapy or with induction chemotherapy followed by concurrent chemoradiation.

*Acceptable chemotherapy regimens for advanced nasopharyngeal cancers (stages II-IVB):*

* Cisplatin 100 mg/m2 IV on days 1, 22, and 43 with radiation +/- adjuvant chemotherapy with cisplatin 80 mg/m2 IV on day 1 plus 5-FU 1000 mg/m2/day by continuous IV infusion on days 1-4 every 4wk for three cycles
* Carboplatin AUC 6 IV every 3 weeks for three cycles with radiation +/- adjuvant chemotherapy with carboplatin AUC 5 IV on day 1 plus 5-FU 1000 mg/m2/day by continuous IV infusion on days 1-4 every 3 weeks for two cycles
* Induction chemotherapy with docetaxel 70 mg/m2 IV on day 1 plus cisplatin 75 mg/m2 IV on day 1 plus 5-FU 1000 mg/m2/day by continuous IV infusion on days 1-4 for three cycles followed by concurrent chemoradiation with cisplatin 100 mg/m2 IV on days 1, 22, and 43
* Induction chemotherapy with docetaxel 75 mg/m2 IV on day 1 plus cisplatin 75 mg/m2 IV on day 1 every 3 weeks for two cycles followed by concurrent chemoradiation with weekly cisplatin 40 mg/m2 IV
* Radiation doses during concurrent chemoradiation are up to 70-72 Gy

### First-line chemotherapy for metastatic or recurrent nasopharyngeal cancers

*Stage IVC:*

* Patients with metastatic nasopharyngeal cancers or recurrent disease (after first-line therapy) are treated with standard platinum-based chemotherapies.
* Single agents can be used if patients cannot tolerate platinum doublets.

*Acceptable chemotherapy regimens in patients with progressing or recurrent nasopharyngeal cancers (unless otherwise stated, goal is to complete four to six cycles):*

* Cisplatin 50-70 mg/m2 IV on day 1 plus gemcitabine 1000 mg/m2 IV on days 1, 8, and 15 every 4wk or
* Cisplatin 75 mg/m2 IV on day 1 plus docetaxel 75 mg/m2 IV on day 1 every 3wk or
* Cisplatin 75 mg/m2 IV on day 1 plus paclitaxel 175 mg/m2 IV on day 1 every 3wk or
* Carboplatin AUC 6 IV on day 1 plus docetaxel 65 mg/m2 IV on day 1 every 3wk or
* Carboplatin AUC 6 IV on day 1 plus paclitaxel 200 mg/m2 IV on day 1 every 3wk or
* Cisplatin 100 mg/m2 IV on day 1 plus 5-FU 1000 mg/m2/day by continuous IV infusion on days 1-4 every 3wk or
* Gemcitabine 1000 mg/m2 IV on days 1, 8, and 15 every 4 wkor
* Gemcitabine 1250 mg/m2 IV on days 1 and 8 every 3wk or
* Carboplatin AUC 5 IV on day 1 every 3 weeks plus cetuximab 400 mg/m2 IV loading dose on day 1, then 250 mg/m2 IV weekly or
* Methotrexate 40 mg/m2 IV weekly (3wk equals one cycle) or
* Paclitaxel 200 mg/m2 IV every 3wk or
* Docetaxel 75 mg/m2 IV every 3wk

### Second- and third-line chemotherapy for metastatic or recurrent nasopharyngeal cancers

*Stage IVC:*

* Second-line chemotherapy is given after disease progression or recurrence following completion of first-line therapy.
* Third-line therapies are given after disease progression or recurrence following completion of first- and second-line therapies.
* Second- and third-line regimens are similar to regimens used as first-line therapy but usually offer lower response rates and survival benefits.
* Patients should be treated with platinum-based chemotherapies if they have not previously received a platinum-based drug.
* Some regimens are typically used in head and neck cancers in general, and others have been specifically studied in nasopharyngeal cancer.

*Acceptable chemotherapy regimens in patients with progressing or recurrent nasopharyngeal cancers after completion of first-line therapy (unless otherwise stated, goal is to complete four to six cycles):*

* Cisplatin 50-70 mg/m2 IV on day 1 plus gemcitabine 1000 mg/m2 IV on days 1, 8, and 15 every 4 wk or
* Cisplatin 75 mg/m2 IV on day 1 plus docetaxel 75 mg/m2 IV on day 1 every 3wk or
* Cisplatin 75 mg/m2 IV on day 1 plus paclitaxel 175 mg/m2 IV on day 1 every 3wk or
* Carboplatin AUC 6 IV on day 1 plus docetaxel 65 mg/m2 IV on day 1 every 3wk or
* Carboplatin AUC 6 IV on day 1 plus paclitaxel 200 mg/m2 IV on day 1 every 3wk or
* Cisplatin 100 mg/m2 IV on day 1 plus 5-FU 1000 mg/m2/day by continuous IV infusion on days 1-4 every 3wk or
* Gemcitabine 1000 mg/m2 IV on days 1, 8, and 15 every 4wk or gemcitabine 1250 mg/m2 IV on days 1 and 8 every 3wkor
* Carboplatin AUC 5 IV on day 1 every 3 weeks plus cetuximab 400 mg/m2 IV loading dose on day 1, then 250 mg/m2 IV weekly or
* Capecitabine 1250 mg/m2 PO BID days 1-14, then off 7 days (3-week period is one cycle) or
* Afatinib 40 mg po daily until disease progression or unacceptable toxicity or
* Methotrexate 40 mg/m2 IV weekly (3wk equals one cycle) or
* Paclitaxel 200 mg/m2 IV every 3wk or
* Docetaxel 75 mg/m2 IV every 3wk or
* Pembrolizumab 200 mg IV q3wk or 400 mg IV q6wk  or
* Nivolumab 240 mg IV q2wk or 480 mg q4wk until disease progression

## **Types of Head and Neck Cancer**

### **Laryngeal Cancer**

Laryngeal cancer affects the larynx, located between the base of the tongue and the trachea. The larynx contains the vocal cords and is involved in breathing, producing sound, and protecting the trachea from food aspiration. Smoking, tobacco use, and heavy alcohol consumption are factors that increase the development of laryngeal cancer.

Symptoms associated with laryngeal cancer include the following:

* Sore throat
* Odynophagia (pain on swallowing)
* Ear pain
* Dysphonia (hoarseness and other changes in voice quality)
* Cervical lymphadenopathy (enlarged lymph nodes in the neck)

Depending on the regions of the head and neck affected by the malignant neoplasm, lymph nodes are involved in approximately 25% to 50% of patients with laryngeal cancer. If there is no lymph node involvement, the prognosis for small laryngeal cancers is good, with cure rates ranging from 75% to 95%. Surgery and/or radiation therapy may be curative for small superficial cancers without lymph node involvement.

The goal of preserving vocal function should be considered when determining treatment.7 Advanced-stage tumors require a combination of radiation therapy and chemotherapy, with or without surgery. The development of a second primary tumor can occur in up to 25% of patients with laryngeal cancer whose primary tumor has been controlled. The risk for recurrence of laryngeal cancer is highest within the first 2 to 3 years of treatment.

### **Hypopharyngeal Cancer**

Hypopharyngeal cancers originate from the bottom part of the throat, extending from the hyoid bone to the cricoid cartilage. Hypopharyngeal cancer is uncommon, with approximately 2500 patients diagnosed in the US annually. Because the symptoms of hypopharyngeal cancer often are not noticeable until it is in the late phase and it metastasizes early, survival rates are the lowest of all head and neck cancers. Risk factors contributing to the development of hypopharyngeal cancer include smoking and tobacco use, heavy alcohol consumption, and nutritional deficiencies.

Symptoms associated with hypopharyngeal cancer include the following8:

* Neck mass
* Dysphagia (difficulty swallowing)
* Odynophagia (painful swallowing)
* Voice change
* Persistent sore throat
* Otalgia (ear pain)
* Dysphonia

Except for cancers identified in the very early stage, treatment for patients with hypopharyngeal cancer has been surgery, usually followed by postoperative radiation therapy.

### **Lip and Oral Cavity Cancer**

Most cancers of the lip and oral cavity originate as squamous cell carcinomas and affect the lip, tongue, gums, lining inside the mouth, floor and the roof of the mouth, and the area behind the wisdom teeth (retromolar trigone). Risk factors for lip and oral cavity cancer include smoking and tobacco use, heavy alcohol consumption, and exposure to ultraviolet light.

Symptoms associated with lip and oral cavity cancer include the following:

* Sore on the mouth or lip
* Lump on the lips or in the mouth
* White or red patch inside the mouth
* Difficulty chewing or swallowing
* Jaw swelling
* Sore throat
* Dysphonia
* Loose teeth or dentures that no longer fit

Regular dental examinations are beneficial for identifying symptoms of lip and oral cavity cancer that often go unnoticed. Early-stage cancers of the lip and oral cavity are highly curable by surgery or radiation therapy. Patients with late-stage tumors may be treated with a combination of surgery and radiation therapy. In their early stages, cancers of the lip and oral cavity have high cure rates ranging from 90% to 100%.

### **Oropharyngeal Cancer**

Oropharyngeal cancer affects the soft palate, walls of the throat, tonsils, and base of the tongue. Most oropharyngeal cancers are squamous cell carcinomas. Risk factors include history of smoking (more than 10 pack-years), tobacco use, heavy alcohol consumption, HPV infection (especially HPV type 16), personal history of head and neck cancer, and betel quid chewing. With the rise in the number of HPV-associated cases, the incidence of oropharyngeal cancer has been steadily increasing.

An estimated 58,450 new patients are expected to be diagnosed with oral and oropharyngeal cancer in the US in 2024, with an anticipated 12,230 deaths. According to researchers who evaluated data from the Surveillance, Epidemiology, and End Results (SEER) program, the prevalence of HPV-negative cancer declined by 50% from 1988 to 2004 (from 2.0 per 100,000 to 1.0 per 100,000), while the rate of HPV-positive oropharyngeal cancers increased by 225% during that same period (from 0.8 per 100,000 to 2.6 per 100,000). In a cross-sectional study of more than 2000 patients, researchers also determined that HPV vaccination prevented 88.2% of oral HPV infections that can cause oral cavity and oropharyngeal cancers, with a prevalence of 0.11% and 1.61% in vaccinated and unvaccinated individuals, respectively.

Symptoms associated with oropharyngeal cancer include the following:

* Persistent sore throat
* Dysphagia (difficulty swallowing)
* Difficulty moving the tongue or opening the mouth fully
* Ear pain
* Lump in the back of the mouth, throat, or neck
* White patch on the tongue or lining of the mouth (leukoplakia)
* Weight loss

Prognosis of oropharyngeal cancer depends on the patient’s HPV status, smoking history, stage of the cancer, and lymph node involvement. HPV-positive oropharyngeal tumors are associated with a better prognosis and have lower likelihood of recurrence. Treatment options for patients with oropharyngeal cancer include surgery, radiation therapy, chemotherapy in different combinations depending on stage and metastasis status, and consideration for preserving speech and swallowing function. The standard of care for oropharyngeal cancer has been surgery and radiation therapy.Chemoradiation therapy with immunotherapy may also be considered, as well as radiation with targeted therapy.

### **Nasopharyngeal Cancer**

Nasopharyngeal cancer affects the nasopharynx, which is a small tubular structure located above the soft palate that connects the nose to the oropharynx. Less than 1 person per 100,000 is diagnosed with nasopharyngeal carcinoma globally each year, with most cases occurring in southern China, Southeast Asia, the Arctic, and the Middle East/North Africa. The higher prevalence of this cancer type among Chinese individuals, especially in South China and South Eastern Asia, is mainly attributed to the nonkeratinizing subtype associated with EBV, which has a characteristic sensitivity to radiotherapy. Risk factors contributing to nasopharyngeal cancer include smoking, heavy alcohol consumption, exposure to EBV, Asian ancestry, and family history.

Symptoms associated with nasopharyngeal cancer include the following:

* Lump in the nose or neck
* Difficulty breathing or speaking
* Diminished hearing
* Tinnitus (ringing in the ears)
* Facial numbness
* Epistaxis (nosebleed)
* Diplopia (double vision)
* Ear infection
* Sore throat
* Headache

Treatment for patients with nasopharyngeal cancer is dependent on the stage of disease. High-dose radiation therapy is the recommended treatment for patients with stage I nasopharyngeal cancer. High-dose radiation therapy combined with chemotherapy is the initial treatment for patients with stages II through IV nasopharyngeal cancer, and chemotherapy is recommended for patients with late-stage nasopharyngeal cancer. Surgery may be considered for patients with persistent or recurrent lymph nodes if the primary tumor site is controlled.

### **Nasal Cavity and Paranasal Sinus Cancer**

Nasal cavity and paranasal sinus cancers are 70% to 80% squamous cell carcinomas that arise from the cells lining the inside of the paranasal sinuses and nasal cavity. As most cancers of the nasal cavity and paranasal sinuses are at advanced stages when first diagnosed, rates of cure are generally poor, at less than 50%.Cancers of the paranasal sinus are most commonly located in the maxillary sinus. Tumors of the nasal cavity are less common. Risk factors contributing to cancers of the nasal cavity and paranasal sinus include smoking, occupational exposure to chemicals or dust, and HPV infection.

Symptoms associated with paranasal sinus and nasal cavity cancer include the following:

* Blocked sinuses
* Headache
* Sinus pain
* Lump or sore inside the nose
* Lump on the face or roof of the mouth
* Numbness or tingling in the face
* Diplopia
* Ear pain
* Epistaxis
* Pain in the upper teeth

A combination of surgery and radiation therapy is recommended for the treatment of patients with most cancers of the nasal cavity and paranasal sinuses. Due to the complexity of the treatment, management should be planned based on the individual, including the tumor’s operability, the size of the affected area, and lymph node involvement. If surgery is warranted, the tumor is removed first to enable drainage of the affected sinus(es), followed by radiation therapy.

### **Salivary Gland Cancer**

Cancer of the salivary gland is a rare type of head and neck cancer that affects the tissues of the major and minor salivary glands. Approximately 70 to 80% of these malignant neoplasms originate from the parotid gland, and the palate is the most common location for minor salivary gland tumors. More than 50% of salivary gland tumors are benign.16 Factors that may contribute to the development of salivary gland tumors include exposure to radiation of the head and neck area and occupational exposure to chemicals or dust.

Symptoms associated with salivary gland cancer include the following:

* Lump in the area of the ear, cheek, jaw, or lip, or inside the mouth
* Numbness or weakness in the face
* Persistent facial pain
* Difficulty swallowing or opening the mouth widely

In many patients, symptoms of salivary gland tumors are not accompanied by pain. Persistent facial pain is highly suggestive of a malignant tumor. Only 10% to 15% of malignant parotid neoplasms present with pain.

Surgery is effective in treatment of patients with early-stage, low-grade, malignant salivary gland tumors. Prognosis is largely dependent on tumor size and is more favorable for tumors in a major salivary gland and less favorable for tumors in the sublingual and minor salivary glands. Patients with large tumors may be treated with surgery followed by radiation therapy.

## **Complications of Systemic Therapy in Head and Neck Cancer**

### **Chemotherapy**

Cytotoxic chemotherapy agents target rapidly dividing cancer cells by inhibiting cell division. Chemotherapy can also affect noncancerous cells in the body that divide quickly, such as those in the digestive tract, hair follicles, and bone marrow, leading to an array of adverse reactions.

Cisplatin. Adverse reactions to cisplatin include toxic effects on the kidneys, neuropathy, myelosuppression, hearing damage, nausea, and vomiting.18

Docetaxel. Adverse reactions to docetaxel include infections, low white blood cell count, low platelet level, anemia, nerve pain, altered sense of taste, labored breathing, inflammation of the lining of the digestive tract, mouth sores, fluid retention, lethargy, pain, nausea, diarrhea, vomiting, constipation, anorexia, alopecia, and skin reactions. The most serious adverse reactions associated with treatment with docetaxel are toxic deaths, hepatic impairment, hematologic effects, enterocolitis and neutropenic colitis, hypersensitivity reactions, fluid retention, second primary cancers, cutaneous reactions, neurologic reactions, eye disorders, and asthenia (weakness).20

### **Targeted Therapy**

Targeted therapy works by inhibiting the activities of specific proteins or genes that are involved in cancer cell growth and survival. However, targeted therapy can also affect healthy cells in the body and cause adverse effects.

Cetuximab. The most common adverse reactions with cetuximab as a single agent or in combination with radiation therapy or chemotherapy are rash, pruritus (itching), nail changes, headache, diarrhea, and infection. The most frequently reported adverse reactions when cetuximab is administered in combination with encorafenib are fatigue, nausea, diarrhea, acneiform rash, abdominal pain, decreased appetite, and joint pain. Severe redness and sores of the mouth, lips, or throat; skin reactions; cardiac dysfunction; and blood electrolyte disturbances were higher for patients receiving combination therapy with cetuximab, radiation, and cisplatin therapy compared with patients receiving radiation and cisplatin and radiation therapy without cetuximab. Cardiac arrest or sudden death occurred in 2% of 208 patients treated with cetuximab and radiation therapy in a clinical study. Serious and sometimes fatal allergic reactions are also possible with this drug.

### **Immunotherapy**

Immunotherapy is a type of cancer treatment that harnesses the power of the immune system to fight cancer cells. However, it can also cause immune-related adverse events and lead to more serious autoimmune reactions.

Pembrolizumab. Acute infusion reactions such as fever, hypotension, hypoxemia, rigor, rash, wheezing, and anaphylaxis can occur during administration of pembrolizumab. Other adverse reactions include colitis, hypophysitis (inflammation of the pituitary gland), pneumonitis, nephritis, hepatitis, thyroid disorders, and severe skin reactions.

Nivolumab. The most frequent serious adverse reactions reported with nivolumab administration are pneumonia, dyspnea, confusion state, vomiting, pleural effusion, and respiratory failure. The most common adverse effects reported with nivolumab administration are fatigue, nausea, rash, decreased appetite, and pruritus.

## **Evolving Trends in Head and Neck Cancer Diagnosis, Treatment, and Management**

To enhance early detection, liquid biopsies—sampling body fluids to identify cancer-related markers—are becoming more popular, alongside advanced genomic sequencing technologies.The addition of immunotherapies to current treatment regimens is currently being explored in research studies. Proton therapy is also on the rise because it delivers radiation with greater precision, sparing healthy cells and reducing adverse effects. Managing treatment-related issues, such as swallowing difficulties and speech impairments, is increasingly emphasized to improve patients’ quality of life. Growing recognition of the psychological impact of cancer and its treatments is leading to more integrated care models. Additionally, artificial intelligence and machine learning are being used to boost diagnostic accuracy, predict treatment responses, and customize treatment plans based on extensive data from imaging and clinical studies.

Hypopharyngeal cancer is a disease in which malignant cells form in the tissues of the hypopharynx, the bottom part of the pharynx – the throat. Most hypopharyngeal cancers form in squamous cells, the thin, flat cells lining the inside of the hypopharynx. The hypopharynx has three different areas. Cancer may be found in one or more of these areas.

The National Cancer Institute (NCI) estimates that about 2,500 cases of hypopharyngeal cancer are diagnosed in the United States each year.

Hypopharyngeal cancer is a type of head and neck cancer. Approximately 71,100 cases of head and neck cancer will be diagnosed in the United States in 2024, and about 16,110 people will die from the cancers, according to the NCI.

Risk factors for hypopharyngeal cancer include the following:

* Smoking tobacco.
* Chewing tobacco.
* Heavy alcohol use.
* Eating a diet without enough nutrients.
* Having Plummer-Vinson syndrome.

### **Hypopharyngeal cancer is a disease in which malignant (cancer) cells form in the tissues of the hypopharynx.**

The hypopharynx is the bottom part of the pharynx. The pharynx is a hollow tube about 5 inches long that starts behind the nose, goes down the neck, and ends at the top of the trachea (windpipe) and esophagus (the tube that goes from the throat to the stomach). Air and food pass through the pharynx on the way to the trachea or the esophagus.

### **Signs and symptoms of hypopharyngeal cancer include a sore throat and ear pain.**

These and other signs and symptoms may be caused by hypopharyngeal cancer or by other conditions. Check with your doctor if you have:

* A sore throat that does not go away.
* Ear pain.
* A lump in the neck.
* Painful or difficult swallowing.
* A change in voice.

### **Tests that examine the throat and neck are used to help diagnose hypopharyngeal cancer and find out whether the cancer has spread.**

The following tests and procedures may be used:

* **Physical exam and health history**: An exam of the body to check general signs of health, including checking for signs of disease, such as lumps or anything else that seems unusual. A history of the patient’s health habits and past illnesses and treatments will also be taken.
* **Physical exam of the throat**: An exam in which the doctor feels for swollen lymph nodes in the neck and looks down the throat with a small, long-handled mirror to check for abnormal areas.
* **Neurological exam**: A series of questions and tests to check the brain, spinal cord, and nerve function. The exam checks a person’s mental status, coordination, and ability to walk normally, and how well the muscles, senses, and reflexes work. This may also be called a neuro exam or a neurologic exam.
* **CT scan (CAT scan)**: A procedure that makes a series of detailed pictures of areas inside the body, such as the head, neck, chest, and lymph nodes, taken from different angles. The pictures are made by a computer linked to an x-ray machine. A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly. This procedure is also called computed tomography, computerized tomography, or computerized axial tomography.

**PET scan (positron emission tomography scan)**: A procedure to find malignant tumor cells in the body. A small amount of radioactive glucose (sugar) is injected into a vein. The PET scanner rotates around the body and makes a picture of where glucose is being used in the body. Malignant tumor cells show up brighter in the picture because they are more active and take up more glucose than normal cells do. A PET scan and CT scan may be done at the same time. This is called a PET-CT.

* PET (positron emission tomography) scan. The patient lies on a table that slides through the PET machine. The head rest and white strap help the patient lie still. A small amount of radioactive glucose (sugar) is injected into the patient's vein, and a scanner makes a picture of where the glucose is being used in the body. Cancer cells show up brighter in the picture because they take up more glucose than normal cells do.
* **MRI (magnetic resonance imaging)**: A procedure that uses a magnet, radio waves, and a computer to make a series of detailed pictures of areas inside the body, such as the head, neck, chest, and lymph nodes. This procedure is also called nuclear magnetic resonance imaging (NMRI).
* **Endoscopy**: A procedure used to look at areas in the throat that cannot be seen with a mirror during the physical exam of the throat. An endoscope (a thin, lighted tube) is inserted through the nose or mouth to check the throat for anything that seems unusual. Tissue samples may be taken for biopsy.
* **Biopsy**: The removal of cells or tissues so they can be viewed under a microscope to check for signs of cancer.
* **Bone scan**: A procedure to check if there are rapidly dividing cells, such as cancer cells, in the bone. A very small amount of radioactive material is injected into a vein and travels through the bloodstream. The radioactive material collects in the bones with cancer and is detected by a scanner.
* **Barium esophagogram**: An x-ray of the esophagus. The patient drinks a liquid that contains barium (a silver-white metallic compound). The liquid coats the esophagus and x-rays are taken.
* **Esophagoscopy**: A procedure to look inside the esophagus to check for abnormal areas. An esophagoscope (a thin, lighted tube) is inserted through the mouth or nose and down the throat into the esophagus. Tissue samples may be taken for biopsy.
* **Bronchoscopy**: A procedure to look inside the trachea and large airways in the lung for abnormal areas. A bronchoscope (a thin, lighted tube) is inserted through the nose or mouth into the trachea and lungs. Tissue samples may be taken for biopsy.

### **Certain factors affect prognosis (chance of recovery) and treatment options.**

Prognosis depends on:

* The stage of the cancer (whether it affects part of the hypopharynx, involves the whole hypopharynx, or has spread to other places in the body). Hypopharyngeal cancer is usually detected in later stages because early signs and symptoms rarely occur.
* The patient's age, sex, and general health.
* The location of the cancer.
* Whether the patient smokes during radiation therapy.

Treatment options depend on:

* The stage of the cancer.
* Keeping the patient's ability to talk, eat, and breathe as normal as possible.
* The patient's general health.

Patients who have had hypopharyngeal cancer are at an increased risk of developing a second cancer in the head or neck. Frequent and careful follow-up is important.

### **Stages of Hypopharyngeal Cancer**

* After hypopharyngeal cancer has been diagnosed, tests are done to find out if cancer cells have spread within the hypopharynx or to other parts of the body.
* There are three ways that cancer spreads in the body.
* Cancer may spread from where it began to other parts of the body.
* The following stages are used for hypopharyngeal cancer:
  + Stage 0 (carcinoma in situ)
  + Stage I
  + Stage II
  + Stage III
  + Stage IV
* After surgery, the stage of the cancer may change and more treatment may be needed.
* Hypopharyngeal cancer can recur (come back) after it has been treated.

### **After hypopharyngeal cancer has been diagnosed, tests are done to find out if cancer cells have spread within the hypopharynx or to other parts of the body.**

The process used to find out if cancer has spread within the hypopharynx or to other parts of the body is called staging. The information gathered from the staging process determines the stage of the disease. It is important to know the stage of the disease in order to plan treatment. The results of some of the tests and procedures used to diagnose hypopharyngeal cancer are often also used to stage the disease.

### **There are three ways that cancer spreads in the body.**

Cancer can spread through tissue, the lymph system, and the blood:

* Tissue. The cancer spreads from where it began by growing into nearby areas.
* Lymph system. The cancer spreads from where it began by getting into the lymph system. The cancer travels through the lymph vessels to other parts of the body.
* Blood. The cancer spreads from where it began by getting into the blood. The cancer travels through the blood vessels to other parts of the body.

### **Cancer may spread from where it began to other parts of the body.**

When cancer spreads to another part of the body, it is called metastasis. Cancer cells break away from where they began (the primary tumor) and travel through the lymph system or blood.

* Lymph system. The cancer gets into the lymph system, travels through the lymph vessels, and forms a tumor (metastatic tumor) in another part of the body.
* Blood. The cancer gets into the blood, travels through the blood vessels, and forms a tumor (metastatic tumor) in another part of the body.

The metastatic tumor is the same type of cancer as the primary tumor. For example, if hypopharyngeal cancer spreads to the lung, the cancer cells in the lung are actually hypopharyngeal cancer cells. The disease is metastatic hypopharyngeal cancer, not lung cancer.

### **The following stages are used for hypopharyngeal cancer:**

The staging described below is only used for patients who have not had lymph nodes in the neck removed and checked for signs of cancer.

#### **Stage 0 (carcinoma in situ)**

In stage 0, abnormal cells are found in the lining of the hypopharynx. These abnormal cells may become cancer and spread into nearby normal tissue. Stage 0 is also called carcinoma in situ.

Tumor sizes are often measured in centimeters (cm) or inches. Common food items that can be used to show tumor size in cm include: a pea (1 cm), a peanut (2 cm), a grape (3 cm), a walnut (4 cm), a lime (5 cm or 2 inches), an egg (6 cm), a peach (7 cm), and a grapefruit (10 cm or 4 inches).

#### **Stage I**

In stage I, cancer has formed in only one area of the hypopharynx and/or the tumor is 2 centimeters or smaller.

#### **Stage II**

In stage II, the tumor is:

* found in more than one area of the hypopharynx or in a nearby area; or
* larger than 2 centimeters but not larger than 4 centimeters and has not spread to the larynx (voice box).

#### **Stage III**

In stage III, the tumor:

* is larger than 4 centimeters or has spread to the larynx (voice box) or the mucosa (inner lining) of the esophagus. Cancer may have spread to one lymph node on the same side of the neck as the tumor. The affected lymph node is 3 centimeters or smaller; or
* has spread to one lymph node on the same side of the neck as the tumor. The affected lymph node is 3 centimeters or smaller. Cancer is also found:
  + in only one area of the hypopharynx and/or the tumor is 2 centimeters or smaller; or
  + in more than one area of the hypopharynx or in a nearby area, or the tumor is larger than 2 centimeters but not larger than 4 centimeters and has not spread to the larynx.

#### **Stage IV**

Stage IV is divided into stages IVA, IVB, and IVC as follows:

* In stage IVA, the tumor:
  + has spread to the thyroid cartilage, the bone above the thyroid cartilage, the thyroid gland, the cartilage around the trachea, the esophageal muscle, or the nearby muscles and fatty tissue in the neck. Cancer may have also spread to one lymph node on the same side of the neck as the tumor. The affected lymph node is 3 centimeters or smaller; or
  + is found in the hypopharynx and may have spread to the thyroid cartilage, the bone above the thyroid cartilage, the thyroid gland, the cartilage around the trachea, the esophagus, or the nearby muscles and fatty tissue in the neck. Cancer has spread to one of the following:
    - one lymph node on the same side of the neck as the tumor. The affected lymph node is larger than 3 centimeters but not larger than 6 centimeters; or
    - more than one lymph node anywhere in the neck. The affected lymph nodes are 6 centimeters or smaller.
* In stage IVB, the tumor:
  + may be any size and cancer may have spread to the thyroid cartilage, the bone above the thyroid cartilage, the thyroid gland, the cartilage around the trachea, the esophagus, or the nearby muscles and fatty tissue in the neck. Cancer has spread to a lymph node that is larger than 6 centimeters or has spread through the outside covering of a lymph node into nearby connective tissue; or
  + has spread to the connective tissue covering the muscles that support the spinal column, the area around the carotid artery, or the area between the lungs. Cancer may have also spread to lymph nodes in the neck.
* In stage IVC, cancer has spread to other parts of the body, such as the lung, liver, or bone.

### **After surgery, the stage of the cancer may change and more treatment may be needed.**

If the cancer is removed by surgery, a pathologist will examine a sample of the cancer tissue under a microscope. Sometimes, the pathologist’s review results in a change to the stage of the cancer and more treatment is needed after surgery.

### **Hypopharyngeal cancer can recur (come back) after it has been treated.**

The cancer may come back in the hypopharynx or in other parts of the body.

### **Treatment Option**

* There are different types of treatment for patients with hypopharyngeal cancer.
* The following types of treatment are used:
  + Surgery
  + Radiation therapy
  + Chemotherapy
  + Immunotherapy
* New types of treatment are being tested in clinical trials.
* Treatment for hypopharyngeal cancer may cause side effects.
* Patients may want to think about taking part in a clinical trial.
* Patients can enter clinical trials before, during, or after starting their cancer treatment.
* Follow-up care may be needed.

### **There are different types of treatment for patients with hypopharyngeal cancer.**

Different types of treatment are available for patients with hypopharyngeal cancer. Some treatments are standard (the currently used treatment), and some are being tested in clinical trials. A treatment clinical trial is a research study meant to help improve current treatments or obtain information on new treatments for patients with cancer. When clinical trials show that a new treatment is better than the standard treatment, the new treatment may become the standard treatment. Patients may want to think about taking part in a clinical trial. Some clinical trials are open only to patients who have not started treatment.

### **The following types of treatment are used:**

#### **Surgery**

Surgery (removing the cancer in an operation) is a common treatment for all stages of hypopharyngeal cancer. The following surgical procedures may be used:

* Laryngopharyngectomy: Surgery to remove the larynx (voice box) and part of the pharynx (throat).
* Partial laryngopharyngectomy: Surgery to remove part of the larynx and part of the pharynx. A partial laryngopharyngectomy prevents loss of the voice.
* Neck dissection: Surgery to remove lymph nodes and other tissues in the neck.

After the doctor removes all the cancer that can be seen at the time of the surgery, some patients may be given chemotherapy or radiation therapy after surgery to kill any cancer cells that are left. Treatment given after the surgery, to lower the risk that the cancer will come back, is called adjuvant therapy.

#### **Radiation therapy**

Radiation therapy is a cancer treatment that uses high-energy x-rays or other types of radiation to kill cancer cells or keep them from growing. External radiation therapy uses a machine outside the body to send radiation toward the area of the body with cancer.

External-beam radiation therapy of the head and neck. A machine is used to aim high-energy radiation at the cancer. The machine can rotate around the patient, delivering radiation from many different angles to provide highly conformal treatment. A mesh mask helps keep the patient’s head and neck from moving during treatment. Small ink marks are put on the mask. The ink marks are used to line up the radiation machine in the same position before each treatment.

Radiation therapy may work better in patients who have stopped smoking before beginning treatment. External radiation therapy to the thyroid or the pituitary gland may change the way the thyroid gland works. A blood test to check the thyroid hormone level in the body may be done before and after therapy to make sure the thyroid gland is working properly.

#### **Chemotherapy**

Chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping the cells from dividing. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy).

Chemotherapy may be used to shrink the tumor before surgery or radiation therapy. This is called neoadjuvant chemotherapy

#### **Immunotherapy**

Immunotherapy is a treatment that uses a person's immune system to fight cancer. Your doctor may suggest biomarker tests to help predict your response to certain immunotherapy drugs. Learn more about Biomarker Testing for Cancer Treatment.

Pembrolizumab and nivolumab are types of immunotherapy used to treat metastatic or recurrent hypopharyngeal cancer.

Treatment of stage I hypopharyngeal cancer may include:

* Laryngopharyngectomy and neck dissection with or without high-dose radiation therapy to the lymph nodes of the neck.
* Partial laryngopharyngectomy with or without high-dose radiation therapy to the lymph nodes on both sides of the neck.

### **Treatment of Stage II Hypopharyngeal Cancer**

Treatment of stage II hypopharyngeal cancer may include:

* Laryngopharyngectomy and neck dissection. High-dose radiation therapy to the lymph nodes of the neck may be given before or after surgery.
* Partial laryngopharyngectomy. High-dose radiation therapy to the lymph nodes of the neck may be given before or after surgery.
* Chemotherapy given during or after radiation therapy or after surgery.
* A clinical trial of chemotherapy followed by radiation therapy or surgery.

### **Treatment of Stage III Hypopharyngeal Cancer**

Treatment of stage III hypopharyngeal cancer may include:

* Radiation therapy before or after surgery.
* Chemotherapy given during or after radiation therapy or after surgery.
* A clinical trial of chemotherapy followed by surgery and/or radiation therapy.
* A clinical trial of surgery followed by chemotherapy given at the same time as radiation therapy.
* A clinical trial of chemotherapy given at the same time as radiation therapy.

Treatment and follow-up of stage III hypopharyngeal cancer is complex and is ideally overseen by a team of specialists with experience and expertise in treating this type of cancer. If all or part of the hypopharynx is removed, the patient may need plastic surgery and other special help with breathing, eating, and talking.

### **Treatment of Stage IV Hypopharyngeal Cancer**

Treatment of stages IVA, IVB, and IVC hypopharyngeal cancer that can be treated with surgery may include:

* Radiation therapy before or after surgery.
* A clinical trial of chemotherapy followed by surgery and/or radiation therapy.
* A clinical trial of surgery followed by chemotherapy given at the same time as radiation therapy.

Surgical treatment and follow-up of stage IV hypopharyngeal cancer is complex and is ideally overseen by a team of specialists with experience and expertise in treating this type of cancer. If all or part of the hypopharynx is removed, the patient may need plastic surgery and other special help with breathing, eating, and talking.

Treatment of stages IVA, IVB, and IVC hypopharyngeal cancer that cannot be treated with surgery may include:

* Radiation therapy.
* Chemotherapy given at the same time as radiation therapy.
* A clinical trial of radiation therapy with chemotherapy.

### **Treatment of Recurrent and Metastatic Hypopharyngeal Cancer**

Treatment of hypopharyngeal cancer that has recurred (come back) or that has spread to other parts of the body may include:

* Surgery.
* Radiation therapy.
* Chemotherapy.
* Immunotherapy (nivolumab or pembrolizumab).
* A clinical trial of chemotherapy.

## 

## **Epidemiology of Squamous Cell Carcinoma (SCC) of the Head and Neck**

Global Incidence and Mortality

* Head and neck squamous cell carcinoma (HNSCC) is the seventh most common cancer worldwide, with approximately 890,000 new cases and 450,000 deaths annually (about 4.5% of all cancer diagnoses and deaths globally).
* The sites involved include the oral cavity, pharynx, hypopharynx, larynx, nasal cavity, and salivary glands.
* Incidence varies widely by region, with the highest rates in South and Southeast Asia, Central and Eastern Europe, and South America.
* In India, tobacco (smoked or chewed) and areca nut (betel quid) use account for up to 80% of cases.

Risk Factors and Trends

* The major risk factors are tobacco use (smoking and chewing), alcohol consumption, and areca nut chewing. Alcohol and tobacco have a synergistic effect, increasing risk up to 40-fold.
* In developed countries, HPV-related HNSCC (particularly oropharyngeal cancers) is rising and now surpasses tobacco- and alcohol-related cases. HPV-positive cancers have better survival rates (median survival ~130 months vs. 20 months for HPV-negative).
* Socioeconomic disparities affect incidence and survival, with higher rates and poorer outcomes among minority and lower socioeconomic groups in developed nations.

Demographics

* Globally, HNSCC is more common in men than women, with a male-to-female ratio around 2–3:1.
* Most patients are diagnosed between 50 and 70 years of age, with a median age around 54–64 years.
* In the United States, approximately 54,000 new cases were diagnosed in 2022, with about 11,230 deaths.
* Incidence rates have declined overall in the US due to reduced tobacco use but have recently increased due to HPV-related disease.

Survival and Mortality

* The 5-year survival rate for HNSCC averages about 50–68%, varying widely by stage and HPV status.
* Survival is better for localized disease (5-year survival ~86%) and worse for metastatic disease (~39%).
* Mortality rates have remained relatively stable globally, with some regional variations.
* Hypopharyngeal cancers have the worst outcomes among HNSCC sites.

Prevention and Public Health

* Smoking and alcohol cessation programs, education on areca nut risks, and HPV vaccination are key prevention strategies.
* HPV vaccination starting at ages 11–12 is effective in reducing HPV-related HNSCC incidence.
* Routine oral screening for high-risk populations can aid early detection and improve outcomes

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## **Differential Diagnosis of Squamous Cell Carcinoma (SCC) of the Head and Neck**

## 1. Malignant Tumors with Similar Features

* Basaloid Squamous Cell Carcinoma  
  A high-grade variant of SCC with distinct histology; must be distinguished from:
  + Adenoid cystic carcinoma
  + Small cell neuroendocrine carcinoma
  + Basal cell adenocarcinoma
  + Adenosquamous carcinoma
  + Spindle cell squamous carcinoma
  + Mucoepidermoid carcinoma
  + Adenoid squamous cell carcinoma  
    (Source: )
* Mucoepidermoid Carcinoma  
  May resemble SCC, especially high-grade forms with squamous differentiation; presence of mucous cells helps differentiation.
* Adenosquamous Carcinoma  
  Contains both squamous and glandular components, requiring careful histological assessment.
* Small Cell Neuroendocrine Carcinoma  
  Distinguished by neuroendocrine markers and aggressive behavior.
* Basal Cell Adenocarcinoma  
  A rare salivary gland malignancy that can mimic SCC histologically.
* Epithelioid Sarcoma and Angiosarcoma  
  Rare tumors that may mimic SCC morphologically but differ in immunohistochemical profiles (e.g., INI1 loss in epithelioid sarcoma, endothelial markers in angiosarcoma).

## 2. Benign and Reactive Conditions

* Pseudoepitheliomatous Hyperplasia (PEH)  
  A benign reactive proliferation of squamous epithelium that can mimic SCC histologically, often seen in chronic inflammation or trauma.
* Granular Cell Tumor  
  May show overlying pseudoepitheliomatous hyperplasia; S100 positive, typically on dorsal tongue—uncommon for SCC.

## 3. Other Head and Neck Malignancies

* Nasopharyngeal Carcinoma  
  Often associated with Epstein-Barr virus (EBV), distinct from typical SCC.
* Lymphomas  
  May present as neck masses; distinguished by immunophenotyping.
* Metastatic Tumors  
  Secondary tumors from other primary sites may mimic SCC.

## **Prevention of Squamous Cell Carcinoma (SCC) of the Head and Neck**

## 1. Avoid Tobacco Use and Promote Smoking Cessation

* Tobacco smoking and chewing are the primary risk factors for HNSCC, increasing risk dramatically, especially when combined with alcohol use.
* Effective prevention includes:
  + Counseling and pharmacotherapy (nicotine replacement, varenicline, bupropion) to help smokers quit.
  + Public health campaigns and community engagement to reduce tobacco use.
  + Recognizing that quitting often requires multiple attempts; combined behavioral and medical support improves success rates.

## 2. Limit Alcohol Consumption

* Heavy alcohol use synergizes with tobacco to increase HNSCC risk up to 40-fold.
* Recommendations include limiting intake to no more than 30 g/day for men and 20 g/day for women.
* Treatment for alcohol use disorder (naltrexone, acamprosate, disulfiram) combined with counseling improves cessation success.
* Targeted public health efforts are needed in high-risk communities with concurrent tobacco and alcohol use.

## 3. Prevent and Treat HPV Infection

* Human papillomavirus (HPV), especially high-risk types, causes a rising proportion of oropharyngeal cancers.
* HPV vaccination starting at ages 11–12 for both boys and girls significantly reduces HPV-related HNSCC risk.
* Safe sex education and vaccination uptake are critical components of prevention.

## 4. Avoid Areca Nut (Betel Quid) Chewing

* Areca nut chewing, common in parts of Asia and among diaspora communities, increases oral cancer risk, especially when combined with tobacco.
* Education and community programs have successfully reduced areca nut use in some populations.

## 5. Maintain Good Oral Hygiene and Regular Screening

* Good oral hygiene and regular dental check-ups help detect precancerous lesions early.
* Routine oral and throat examinations are recommended for high-risk individuals (tobacco/alcohol users, HPV-positive patients).
* While general population screening is not proven effective, targeted screening in high-risk groups may reduce late-stage diagnoses.

## 6. Healthy Diet and Lifestyle

* Diets rich in fruits, vegetables, and antioxidants (e.g., curcumin, green tea) may reduce risk.
* Avoid excessive intake of red and processed meats, fried foods, and salted fish, which may increase risk.
* Maintaining a healthy weight and avoiding nutritional deficiencies supports overall cancer prevention.

## 7. Public Health and Community Engagement

* Tailored interventions in minority and low socioeconomic groups improve awareness and reduce disparities.
* Engaging community leaders (e.g., pastors, barbers) has proven effective in some populations.
* Policies to reduce tobacco and alcohol availability and use are essential.

## **Genomic Alterations**

* Commonly Amplified Genes:
  + *PIK3CA* (phosphatidylinositol 3-kinase catalytic subunit alpha)
  + *EGFR* (epidermal growth factor receptor)
  + *CCND2* (cyclin D2)
  + *ERBB2* (HER2)
  + *FGFR1* (fibroblast growth factor receptor 1)
  + *E2F1* (cell cycle regulator)
* Frequently Deleted or Inactivated Genes:
  + *CDKN2A* (tumor suppressor regulating cell cycle)
  + *TP53* (tumor suppressor gene, especially in HPV-negative tumors)
  + *NOTCH1* and *NOTCH2* (involved in cell differentiation)
  + *SMAD4* (TGF-β signaling)
  + *TRAF3* (deleted particularly in HPV-positive tumors)
* Mutational Differences by HPV Status:
  + HPV-positive tumors often harbor activating mutations in *PIK3CA* and loss of *TRAF3*, with fewer *TP53* mutations. They show distinct genomic profiles with better prognosis.
  + HPV-negative tumors frequently have loss-of-function mutations in *TP53* and *CDKN2A*, along with widespread copy number alterations (amplifications of 3q26/28 and 11q13/22).
* Other Notable Mutations:
  + *HRAS* and *CASP8* mutations occur in a subgroup of oral cavity tumors.
  + Mutations in chromatin modifiers like *NSD1*, and WNT pathway genes (*AJUBA*, *FAT1*) are found mainly in laryngeal tumors.
  + Activation of oxidative stress factor *NFE2L2* is also observed.

## 2. Mutation Burden and Patterns

* Mutation loads vary by anatomical site, with laryngeal carcinomas showing the highest mutation burden.
* HPV-positive tumors have a higher frequency of oncogene (OG) alterations compared to tumor suppressor gene (TSG) alterations.
* HPV-negative tumors have a predominance of TSG mutations, especially *TP53*.

## 3. Therapeutic Implications

* Alterations in the EGFR/PI3K pathway (e.g., *PIK3CA* mutations) are potential predictive biomarkers for targeted therapies.
* Identification of actionable mutations through genomic profiling can guide personalized treatment strategies, including targeted agents and immunotherapy.
* Fusion events such as *TEX10-NTRK2* may provide opportunities for treatment with TRK inhibitors (e.g., larotrectinib).

## **Squamous Cell Carcinoma (SCC) of the Head and Neck: Question and Answer Set**

Q1: What causes head and neck squamous cell carcinoma?  
A: The main causes are tobacco use (smoking and chewing) and alcohol consumption. Human papillomavirus (HPV) infection, especially HPV-16, is also a significant cause, particularly for oropharyngeal cancers.

Q2: Where does head and neck squamous cell carcinoma typically arise?  
A: SCC arises from squamous cells lining the moist mucosal surfaces of the head and neck, including the oral cavity, nasal cavity, paranasal sinuses, pharynx, and larynx.

Q3: Can squamous cells be found in lymph nodes without a known primary tumor?  
A: Yes, this is called metastatic squamous neck cancer with unknown (occult) primary when squamous cells are found in upper neck lymph nodes without an identified primary tumor.

Q4: What is the most common HPV subtype associated with periungual and some head and neck SCCs?  
A: HPV subtype 16 is the most commonly associated with periungual SCC and many HPV-related head and neck cancers.

Q5: What factors increase the risk of metastasis in SCC of the head and neck?  
A: Larger tumor size (>2 cm), perineural invasion, immunosuppression, certain histological types (e.g., desmoplastic, spindle cell), and tumor depth increase the risk of metastasis.

Q6: What is the most common site for SCC metastasis risk in the head and neck region?  
A: The ear has the greatest risk of metastasis (~14%), slightly higher than the lip (~11%).

Q7: What is the recommended surgical margin for melanomas more than 2 mm in thickness?  
A: Wide local excision with a margin of 2 cm is recommended for melanomas thicker than 2 mm; margins vary for other skin cancers but are important for SCC surgical planning.

Q8: What is the overall increased risk of developing cutaneous malignancies in organ transplant recipients?  
A: Organ transplant recipients have a 3–4 times higher risk of malignancies, with cutaneous SCC risk increased approximately 65-fold compared to the general population.

Q9: What is the significance of early detection in head and neck SCC?  
A: Early diagnosis improves survival rates and reduces morbidity by allowing for less extensive treatment and better functional outcomes.

Q10: What preventive measures can reduce the risk of head and neck SCC?  
A: Avoiding tobacco and alcohol, HPV vaccination, limiting sun exposure, and maintaining good oral hygiene are key preventive strategies.

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**TRANSITION CELL CARCINOMA**

### **Urothelial carcinoma**

Urothelial carcinoma is cancer that starts in your urothelium, the tissue that lines parts of your urinary system. Urothelial carcinoma accounts for about 90% of all cases of bladder cancer and 7% of all cases of kidney cancer, including cancer in your renal pelvis and ureter. Bladder and kidney cancers caused by urothelial carcinoma have similar symptoms. They also have similar prognoses — caught early on, these cancers are easily treated, but often come back.

Urothelial carcinoma may affect your bladder and kidneys in different ways.

##### **Urothelial carcinoma in your bladder**

Your bladder is a triangle-shaped organ that’s centered between your hip bones, above your urethra and below your kidneys. Pee (urine) from your kidneys drains into your bladder, which is lined with tissue called urothelium. Urothelium is made of cells that stretch when your bladder fills with pee and collapses when it’s empty. (Your bladder can hold about 2 cups of pee.)

In bladder cancer, abnormal urothelial cells spread from the inner lining to other layers deep in your bladder. The abnormal cells may also spread through your bladder wall into the fatty tissues that surround your bladder. Left untreated, bladder cancer may grow through your bladder walls to nearby lymph nodes and then other areas of your body, including your bones, lungs or liver.

Bladder cancer can be high-grade or low-grade:

* High-grade urothelial carcinoma may be life-threatening. It often comes back after treatment. It may spread into the muscle layer of your bladder, to other areas in your body and to your lymph nodes.
* Low-grade urothelial carcinoma may come back (recur), but rarely spreads into your bladder’s muscle layer or other parts of your body.

##### **Urothelial carcinoma in your kidneys**

Most people have two kidneys. Kidneys are bean-shaped organs that sit just below your rib cage and behind your belly. Your kidneys clear toxins and waste from your blood by producing pee (urine) that collects in your renal pelvis located in the middle of each kidney. From there, your pee drains through a long tube that connects your kidney to your bladder. This tube is your ureter. Like your kidneys, your renal pelvis and ureter are lined with urothelial tissue.

In kidney cancer, abnormal urothelial cells form tumors in your kidneys, renal pelvis or ureter. Kidney cancer may spread to other organs or tissues.

Bladder cancer is the sixth most common cancer in the U.S. Urothelial bladder cancer represents 90% of all cases of bladder cancers. You're four times more likely to get bladder cancer if you're male.

Kidney cancer is the eighth most common cancer. Urothelial kidney cancer represents about 7% of all kidney cancers. Kidney cancer is most common in people between the ages of 65 and 74. Males are twice as likely to develop the disease.

## **Symptoms and Causes**

Urothelial carcinoma may not cause symptoms right away. In general, blood in your pee (urine) is the first noticeable symptom. You should contact a healthcare provider if you notice blood in your pee or other symptoms, including:

* Persistent back pain.
* Tiredness.
* Unexplained weight loss.
* Painful urination (dysuria).
* A lump or mass in your kidney area.
* Low-grade fever.

### **What causes urothelial carcinoma?**

Medical researchers aren’t sure exactly what causes urothelial carcinoma in your bladder and kidneys. But they have identified some common risk factors:

* Cigarette smoke: Smoking cigarettes increases your risk of developing urinary system cancers linked to urothelial carcinoma.
* Exposure to certain chemicals: Studies show that people who work with certain chemicals used in dyes, rubber, leather, paint, some textiles and hairdressing supplies may have an increased risk of urinary system cancers linked to urothelial carcinoma.

## **Diagnosis and Tests**

Healthcare providers may use the following tests to diagnose bladder and kidney cancer, including urothelial carcinoma. Tests include:

* Urinalysis: A test to check the color of your pee (urine) and its contents, such as sugar, protein, blood and bacteria.
* Urine cytology: Healthcare providers examine your pee under a microscope to check for abnormal cells. Cancer in your kidneys, bladder or ureter may shed cancer cells into your urine.
* Intravenous pyelogram (IVP): A series of X-rays of your kidneys, ureter and bladder to check for cancer. Healthcare providers inject a contrast dye into one of your veins. Then, they take X-rays as the dye moves through your kidneys, ureter and bladder to see if there are any blockages.
* Ureteroscopy: Providers use a thin tube-like instrument with a light and lens for viewing to look inside your ureter and renal pelvis and to take tissue samples.
* Computed tomography (CT scan): CT scans use a computer linked to an X-ray machine to make a series of detailed pictures of areas inside your body. This procedure is also called computerized tomography, or computerized axial tomography.
* Ultrasound: A procedure in which high-energy sound waves (ultrasound) are bounced off internal tissues or organs and make echoes. The echoes form a picture of body tissues called a sonogram. Healthcare providers may do an abdominal ultrasound to help diagnose cancer of your renal pelvis and ureter.
* Magnetic resonance imaging (MRI): A procedure that uses a magnet, radio waves and a computer to make a series of detailed pictures of areas inside your body, such as your pelvis. This procedure is also called nuclear magnetic resonance imaging (NMRI).

#### **Cancer staging**

Healthcare providers use a cancer staging system to develop treatment plans and establish prognoses or expected outcomes. Cancer staging describes how tumors are growing or spreading.

Cancer staging is a complicated process to complete, much less explained. It’s understandable if you feel intimidated, confused or unnerved by a process that seems to reduce your illness to a formula of letters and numbers. Your providers understand why you may feel this way. If you’re confused or concerned by what you’re hearing, ask your provider to explain how the cancer staging system works in your situation.

##### **Bladder cancer stages**

Bladder cancer can be either early stage (confined to the lining of your bladder) or invasive (penetrating your bladder wall and possibly spreading to nearby organs or lymph nodes). Bladder cancer stages are:

* Stage I: Cancer is confined to the lining of your bladder or the connective tissue just below the lining, but hasn’t invaded the main muscle wall of your bladder.
* Stage II: Cancer has spread to the muscle wall of your bladder.
* Stage III: Cancer has spread to the fatty tissue outside of your bladder muscle.
* Stage IV: Cancer has spread from your bladder to your lymph nodes or to other organs or bones.

Healthcare providers may also categorize bladder cancer as being noninvasive, non-muscle-invasive or muscle-invasive.

* Noninvasive: This bladder cancer may be tumors in a small section of tissue or cancer that’s only on or near the surface of your bladder.
* Non-muscle-invasive: This refers to bladder cancer that’s moved deeper into your bladder but hasn’t spread to muscle.
* Muscle-invasive: This bladder cancer has grown into your bladder wall muscle and may have spread into the fatty layers or tissues on organs outside of your bladder.

##### **Kidney cancer stages**

Healthcare providers don’t break out kidney cancer stages by type of cancer cell. Urothelial carcinoma represents about 7% of all kidney cancers. Kidney cancer and cancer in your renal pelvis and ureter have different cancer stages.

* Stage I: Cancer hasn’t spread from your kidney.
* Stage II: Cancer has grown but hasn’t spread from your kidney.
* Stage III: Cancer has spread from your kidney to your major blood vessels — your renal vein and inferior vena cava — or into the tissue surrounding your kidney or to nearby lymph nodes.
* Stage IV: Cancer has spread from your adrenal gland (the small gland that sits on top of your kidney) or to distant lymph nodes or other organs.

##### **Renal pelvis and ureter cancer stages**

* Stage 0: There are abnormal cells in tissue lining your renal pelvis or ureter. This cancer stage may be called papillary carcinoma or carcinoma in situ.
* Stage 1: Cancer spreads through the lining of your renal pelvis and/or ureter into a layer of connective tissue.
* Stage II: Cancer has spread through connective tissue to your renal pelvis and/or ureter’s layer of muscle.
* Stage IV: Cancer spreads to nearby organs, one or more lymph nodes, the layer of fat around your kidney or more distant organs such as your lung, liver or bones.

## **Management and Treatment**

Healthcare providers have different treatments for urothelial carcinoma in your bladder, kidneys, renal pelvis and ureter. Urothelial carcinoma causes 90% of all bladder cancer and 7% of all types of kidney cancer, including cancer in your renal pelvis and ureter.

#### **Bladder cancer treatment**

Treatment may include:

* Surgery. Surgeons either remove the tumor or use high-energy electricity to burn it away with a process known as fulguration.
* Chemotherapy.
* Immunotherapy.
* Radiation therapy.
* Targeted therapy.

#### **Kidney cancer treatment**

Healthcare providers treat kidney cancer with many of the same treatments they use for bladder cancer. Additional treatments may include:

* Surgery. Surgeons may remove the part of your kidney that contains cancer. They may also remove your entire kidney.
* Cryoablation.
* Radiofrequency ablation.

#### **Renal pelvis and/or ureter cancer treatment**

* Surgery. Surgeons remove the part of your renal pelvis or ureter that contains cancer.

## **Outlook / Prognosis**

Urothelial carcinoma is cancer that starts in cells that line your bladder, your kidneys, renal pelvis and ureter. While the same cancerous cell causes these cancers, each cancer type has different prognoses or expected outcomes.

#### **Bladder cancer prognosis**

Like many types of cancer, early detection and treatment increase the chance of living longer with bladder cancer. According to 2018 data from the National Cancer Institute (NCI), 96% of people who received treatment for early-stage cancer were alive five years after diagnosis. Overall, 77% of people with bladder cancer were alive five years after diagnosis.

#### **Kidney cancer prognosis**

Like most cancers, kidney cancer, including renal pelvis cancer, is most treatable when found in its early stages. NCI data from 2018 show 93% of people treated for early-stage kidney cancer were alive five years after diagnosis. The overall five-year survival rate was 76.5%.

## **Prevention**

You may reduce your risk of developing these cancers by not smoking cigarettes and avoiding certain chemicals.

## **Living With**

If cancer is caught in early stages, healthcare providers can often cure urothelial carcinoma that affects your urinary system. Unfortunately, these types of cancer often come back. If you’ve been treated for one of these cancers, you should do your best to be vigilant about follow-up care.

### **When should I see my healthcare provider?**

You should see your healthcare provider any time you have changes in your body that may indicate urothelial cancer in your urinary system has come back.

## **Urothelial Carcinoma Stages**

“Staging refers to the location of the cancer and is typically described as local (in the bladder or ureter only), regional (spread to nearby lymph nodes), or distant (spread to far away lymph nodes or to other organs like lung, liver, bones). Treatment is determined by the stage and grade/type of the cancer,”

Here are the stages of urothelial carcinoma or transitional cell carcinoma:

Stage 0 urothelial carcinoma is located only in the lining of the bladder and has not spread into the muscle or anywhere else. Stage 0 urothelial carcinomas come in two types: 0a and 0is. Stage 0a, noninvasive papillary carcinoma, is the kind that grows into the bladder in finger-like shapes. Stage 0is, urothelial carcinoma in situ, is a flat tumor on the lining of the bladder.

Stage I urothelial carcinoma has spread, but only into the connective tissue that lies under the bladder lining and not into the muscle.

Stage II urothelial carcinoma is also called muscle invasive bladder cancer because the tumor has gone beyond the connective tissue into the muscle beneath it.

Stage III urothelial carcinoma has grown further into the body but has stayed in the general area of the bladder. It is also called “locally advanced urothelial carcinoma” and is divided into stage IIIA and stage IIIB.

* Stage IIIA urothelial carcinoma has spread beyond the muscle and into the layer of fat that surrounds it. It may also have spread to reproductive organs including the prostate, uterus, or vagina or to just one lymph node in the pelvis.
* Stage IIIB urothelial carcinoma has either spread to two lymph nodes or one lymph node that is near blood vessels that bring blood to other parts of the body.

Having cancer cells in more than one lymph node or in lymph nodes near these important arteries means that the cancer is spreading deeper into the body.

Stage [IV](https://www.webmd.com/a-to-z-guides/immunoglobulin-therapy) urothelial carcinoma is also called metastatic urothelial carcinoma. Metastatic means that the cancer has travelled far from where it started in the body. Stage IV also has two substages: IVA and IVB. Five percent of newly diagnosed bladder cancers are metastatic.

* Urothelial carcinoma stage IVA has traveled to distant lymph nodes or into the abdominal wall, which is made up of muscles, fat, and tissues and protects the organs inside your abdomen or the pelvic wall, which protects the organs in your pelvis.
* Urothelial carcinoma stage IVB has spread to one or more organs in completely different regions of the body such as the lungs or bones.

## **Epidemiology of Urothelial Carcinoma (UC)**

## Incidence and Distribution

* Bladder cancer (BC) accounts for 90–95% of urothelial carcinomas, while upper tract urothelial carcinoma (UTUC) (in renal pelvis and ureters) accounts for about 5–10% of cases.
* The annual incidence of UC in Western countries is approximately 2 cases per 100,000 inhabitants, with bladder cancer being much more common than UTUC.
* Globally, bladder cancer incidence was estimated at ~550,000 new cases in 2018 and 573,000 in 2020, making it about 3% of all new cancer diagnoses worldwide.
* In the United States, about 80,000–85,000 new bladder cancer cases are diagnosed annually, making it the sixth most common cancer.

## Demographics

* UC incidence increases with age, peaking between 70 and 90 years.
* It is more common in men than women, with a male-to-female ratio of approximately 2:1 for UTUC and similar or slightly higher for bladder cancer.
* Smoking is a major risk factor, with over 50% of UTUC patients being former or current smokers.

## Geographic Variation

* Highest bladder cancer rates are reported in Southern and Western Europe and North America.
* Countries like Greece (men) and Lebanon (women) have some of the highest incidence rates.
* Lower incidence is found in regions with lower industrial exposure and tobacco use, such as parts of Africa and Central America.

## Trends Over Time

* Incidence rates have generally risen in some European countries due to aging populations and smoking prevalence but have declined in others like New Zealand due to prevention efforts.
* Improved detection techniques and aging populations contribute to increased reported incidence, especially for UTUC.

## Disease Characteristics at Diagnosis

* Approximately two-thirds of UTUC patients present with muscle-invasive disease, compared to 15–25% in bladder cancer.
* Around 25% of UTUC patients have metastasis at diagnosis.
* UTUC can occur metachronously or synchronously with bladder cancer in some patients.

## Risk Factors

* Cigarette smoking and occupational chemical exposures are the main risk factors for both bladder cancer and UTUC.
* Specific regional factors include Balkan endemic nephropathy and Chinese herb nephropathy for UTUC.
* In some regions like Egypt, Schistosoma haematobium infection was historically a major cause of bladder cancer

## **Urothelial Carcinoma: Question and Answer Set**

Q1: What is urothelial carcinoma?  
A: Urothelial carcinoma (also called transitional cell carcinoma) is a malignant tumor arising from the urothelial (transitional) cells lining the urinary tract, most commonly in the bladder but also in the renal pelvis, ureters, and urethra.

Q2: What is the most common symptom of urothelial carcinoma?  
A: Painless hematuria (blood in the urine) is the most common and often first symptom.

Q3: What are the main risk factors for urothelial carcinoma?  
A:

* Cigarette smoking
* Occupational exposure to chemicals (e.g., dyes, rubber, paints, diesel, gas)
* Chronic inflammation or infection
* Prior pelvic radiation
* Certain genetic factors (e.g., FGFR3 mutations).

Q4: What is the definitive diagnostic test for urothelial carcinoma?  
A: Cystoscopy with biopsy is the gold standard for diagnosis.

Q5: What is the lining of the urinary tract called where urothelial carcinoma arises?  
A: Urothelium (transitional epithelium).

Q6: What is the purpose of intravesical BCG therapy?  
A: BCG (Bacillus Calmette-Guérin) is used in intravesical therapy to reduce recurrence and progression of non-muscle-invasive bladder cancer by stimulating a local immune response in the bladder.

Q7: What is the primary goal of transurethral resection of bladder tumor (TURBT)?  
A: To remove visible tumors from the bladder and obtain tissue for diagnosis and staging.

Q8: What are the main types of urothelial carcinoma based on grade and depth?  
A:

* Non-muscle-invasive (confined to urothelium or lamina propria)
* Muscle-invasive (invades the muscularis propria)
* Low-grade (less aggressive) and high-grade (more aggressive).

Q9: What is a primary prevention strategy for urothelial carcinoma?  
A: Smoking cessation and reducing exposure to occupational chemicals.

Q10: What is the benefit of low-grade urothelial carcinoma?  
A: Low-grade tumors are less likely to invade muscle, metastasize, or recur after treatment.

Q11: What is the main concern for nursing care in the first weeks after bladder cancer surgery?  
A: Extreme weight loss and maintaining tissue integrity.

Q12: What is the purpose of irrigating a neobladder after surgery?  
A: To ensure the neobladder remains patent (open) and to prevent blockage by mucus or blood clots.

Q13: What is the main goal of radiation therapy in bladder cancer?  
A: To control local tumor growth, especially in patients who are not surgical candidates.

Q14: What is the significance of multifocal tumors in the bladder?  
A: Multifocality means more than one tumor arises from a single original tumor, which may increase the risk of recurrence.

Q15: What is the benefit of genetic testing in urothelial carcinoma?  
A: It can help identify hereditary cancer risk, guide surveillance, and inform targeted therapy decisions.

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[Urothelial Carcinoma (Transitional Cell Carcinoma)](https://my.clevelandclinic.org/health/diseases/6239-transitional-cell-cancer#overview)

**DUCTAL CARCINOMA IN SITU(BREAST)**

**DEFINITION AND DESCRIPTION**

Ductal carcinoma in situ is a very early form of breast cancer. In ductal carcinoma in situ, the cancer cells are confined inside a milk duct in the breast. The cancer cells haven't spread into the breast tissue. Ductal carcinoma in situ is often shortened to DCIS. It's sometimes called noninvasive, preinvasive or stage 0 breast cancer.

DCIS is usually found during a mammogram done as part of breast cancer screening or to investigate a breast lump. DCIS has a low risk of spreading and becoming life-threatening. However, it does require an evaluation and a consideration of treatment options.

Treatment for DCIS often involves surgery. Other treatments may combine surgery with radiation therapy or hormone therapy.

**Causes**

It's not clear what causes ductal carcinoma in situ, also called DCIS.

This early form of breast cancer happens when cells inside a breast duct develop changes in their DNA. A cell's DNA holds the instructions that tell the cell what to do. In healthy cells, the DNA gives instructions to grow and multiply at a set rate. The instructions tell the cells to die at a set time. In cancer cells, the DNA changes give different instructions. The changes tell the cancer cells to make many more cells quickly. Cancer cells can keep living when healthy cells would die. This causes too many cells.

In DCIS, the cancer cells don't yet have the ability to break out of the breast duct and spread into the breast tissue.

Healthcare professionals don't know exactly what causes the changes in the cells that lead to DCIS. Factors that may play a part include lifestyle, environment and DNA changes that run in families.

**Risk factors**

Several factors may increase the risk of ductal carcinoma in situ, also called DCIS. DCIS is an early form of breast cancer. Risk factors for breast cancer may include:

* **A family history of breast cancer.** If a parent, sibling or child had breast cancer, your risk of breast cancer is increased. The risk is higher if your family has a history of getting breast cancer at a young age. The risk also is higher if you have multiple family members with breast cancer. Still, most people diagnosed with breast cancer don't have a family history of the disease.
* **A personal history of breast cancer.** If you've had cancer in one breast, you have an increased risk of getting cancer in the other breast.
* **A personal history of breast conditions.** Certain breast conditions are a sign of a higher risk of breast cancer. These conditions include lobular carcinoma in situ, also called LCIS, and atypical hyperplasia of the breast. If you've had a breast biopsy that found one of these conditions, you have an increased risk of breast cancer.
* **Beginning your period at a younger age.** Beginning your period before age 12 increases the risk of breast cancer.
* **Beginning menopause at an older age.** Beginning menopause after age 55 increases the risk of breast cancer.
* **Being female.** Women are much more likely than men are to get breast cancer. Everyone is born with some breast tissue, so anyone can get breast cancer.
* **Dense breast tissue.** Breast tissue is made up of fatty tissue and dense tissue. Dense tissue is made of milk glands, milk ducts and fibrous tissue. If you have dense breasts, you have more dense tissue than fatty tissue in your breasts. Having dense breasts can make it harder to detect breast cancer on a mammogram. If a mammogram shows that you have dense breasts, your risk of breast cancer is increased. Talk with your healthcare team about other tests you might have in addition to mammograms to look for breast cancer.
* **Drinking alcohol.** Drinking alcohol increases the risk of breast cancer.
* **Having your first child at an older age.** Giving birth to your first child after age 30 may increase the risk of breast cancer.
* **Having never been pregnant.** Having been pregnant one or more times lowers the risk of breast cancer. Never having been pregnant increases the risk.
* **Increasing age.** The risk of breast cancer goes up as you get older.
* **Inherited DNA changes that increase cancer risk.** Certain DNA changes that increase the risk of breast cancer can be passed from parents to children. The most well-known changes are called BRCA1 and BRCA2. These changes can greatly increase your risk of breast cancer and other cancers, but not everyone with these DNA changes gets cancer.
* **Menopausal hormone therapy.** Taking certain hormone therapy medicines to control the symptoms of menopause may increase the risk of breast cancer. The risk is linked to hormone therapy medicines that combine estrogen and progesterone. The risk goes down when you stop taking these medicines.
* **Obesity.** People with obesity have an increased risk of breast cancer.
* **Radiation exposure.** If you received radiation treatments to your chest as a child or young adult, your risk of breast cancer is higher.

**Symptoms**

Ductal carcinoma in situ doesn't typically cause symptoms. This early form of breast cancer also is called DCIS.

DCIS can sometimes cause symptoms such as:

* A breast lump.
* Bloody nipple discharge.

DCIS is usually found on a mammogram. It appears as tiny flecks of calcium in the breast tissue. These are calcium deposits, often referred to as calcifications.

### **When to see a doctor**

Make an appointment with your doctor or other healthcare professional if you notice a change in your breasts. Changes to look for may include a lump, an area of puckered or otherwise unusual skin, a thickened region under the skin, and nipple discharge.

Ask your healthcare professional when you should consider breast cancer screening and how often it should be repeated. Most healthcare professionals recommend considering routine breast cancer screening beginning in your 40s.

**DIAGNOSIS**

Ductal carcinoma in situ, also called DCIS, is most often discovered during a mammogram used to screen for breast cancer. A mammogram is an X-ray of the breast tissue. If your mammogram shows something concerning, you will likely have additional breast imaging and a biopsy.

### **Mammogram**

If an area of concern was found during a screening mammogram, you may then have a diagnostic mammogram. A diagnostic mammogram takes views at higher magnification from more angles than a mammogram used for screening. This examination evaluates both breasts.

A diagnostic mammogram gives your healthcare team a closer look at any calcium deposits detected in the breast tissue. Calcium deposits, also called calcifications, can sometimes be cancerous.

If the area of concern needs further evaluation, the next step may be an ultrasound and a breast biopsy.

### **Breast ultrasound**

Ultrasound uses sound waves to make images of structures inside the body. A breast ultrasound may give your healthcare team more information about an area of concern. The healthcare team uses this information to decide what tests you might need next.

### **Removing breast tissue samples for testing**

A biopsy is a procedure to remove a sample of tissue for testing in a lab. For DCIS, a healthcare professional removes the sample of breast tissue using a special needle. The needle used is a hollow tube. The healthcare professional puts the needle through the skin on the breast and into the area of concern. The health professional draws out some of the breast tissue. This procedure is called a core needle biopsy.

Often the healthcare professional uses an imaging test to help guide the needle to the right spot. A biopsy that uses ultrasound is called an ultrasound-guided breast biopsy. If it uses X-rays, it's called a stereotactic breast biopsy. The tissue samples are sent to a lab for testing.

In a lab, a doctor who specializes in analyzing blood and body tissue looks at the tissue samples. This doctor is called a pathologist. The pathologist can tell whether cancer cells are present and if so, how aggressive those cells appear to be.

**TREATMENT**

Ductal carcinoma in situ can often be cured. Treatment for this very early form of breast cancer often involves surgery to remove the cancer. Ductal carcinoma in situ, also called DCIS, also may be treated with radiation therapy and medicines.

DCIS treatment has a high likelihood of success. In most instances, the cancer is removed and has a low chance of coming back after treatment.

In most people, treatment options for DCIS include:

* Breast-conserving surgery, called a lumpectomy, and radiation therapy.
* Breast-removing surgery, called a mastectomy.

In some people, treatment options may include:

* Lumpectomy only.
* Lumpectomy and hormone therapy.

### **Surgery**

If you're diagnosed with DCIS, one of the first decisions you'll have to make is whether to treat the condition with lumpectomy or mastectomy.

* **Lumpectomy.** A lumpectomy is surgery to remove breast cancer and some of the healthy tissue around it. The rest of the breast tissue isn't removed. Other names for this surgery are breast-conserving surgery and wide local excision. Most people who have a lumpectomy also have radiation therapy.  
  Research suggests that there is a slightly higher risk of the cancer coming back after lumpectomy compared to mastectomy. However, survival rates between the two treatment approaches are very similar.  
  If you have other serious health conditions, you might consider other options, such as lumpectomy plus hormone therapy, lumpectomy alone or no treatment.
* **Mastectomy.** A mastectomy is surgery to remove all breast tissue from a breast. Breast reconstruction to restore the appearance of the breast can be done at the same time or in a later procedure, if you desire.

Lumpectomy is a good option for most people with DCIS. But mastectomy may be recommended if:

* **You have a large area of DCIS.** If the area is large relative to the size of your breast, a lumpectomy may not produce acceptable cosmetic results.
* **There's more than one area of DCIS.** When there are multiple areas of DCIS, it is called multifocal or multicentric disease. It's difficult to remove multiple areas of DCIS with a lumpectomy. This is especially true if DCIS is found in different parts of the breast.
* **Biopsy results show cancer cells at or near the edge of the tissue sample.** There may be more DCIS than originally thought. This means that a lumpectomy might not be enough to remove all areas of DCIS. A mastectomy could be needed to remove all of the breast tissue.
* **You're not a candidate for radiation therapy.** Radiation is usually given after a lumpectomy. Radiation might not be an option if you're in the first trimester of pregnancy or if you've received radiation to your chest or breast in the past. It also might not be recommended if you have a condition that makes you more sensitive to radiation side effects, such as systemic lupus erythematosus.
* **You prefer to have a mastectomy.** For instance, you might not want a lumpectomy if you don't want to have radiation therapy.

Because DCIS is noninvasive, surgery typically doesn't involve the removal of lymph nodes from under your arm. The chance of finding cancer in the lymph nodes is extremely small.

If your healthcare team thinks the cancer cells may have spread outside the breast duct or if you are having a mastectomy, then some lymph nodes may be removed as part of the surgery.

### **Radiation therapy**

Radiation therapy treats cancer with powerful energy beams. The energy can come from X-rays, protons or other sources.

For DCIS treatment, the radiation is often external beam radiation. During this type of radiation therapy, you lie on a table while a machine moves around you. The machine directs radiation to precise points on your body. Less often, the radiation can be placed inside the body. This type of radiation is called brachytherapy.

Radiation therapy is often used after lumpectomy to reduce the chance that DCIS will come back or that it will progress to invasive cancer. But it might not be necessary if you have only a small area of DCIS that is considered slow-growing and was completely removed during surgery.

### **Hormone therapy**

Hormone therapy, also called endocrine therapy, uses medicines to block certain hormones in the body. It's a treatment for breast cancers that are sensitive to the hormones estrogen and progesterone. Healthcare professionals call these cancers estrogen receptor positive and progesterone receptor positive. Cancers that are sensitive to hormones use the hormones as fuel for their growth. Blocking the hormones can cause the cancer cells to shrink or die.

For DCIS, hormone therapy is typically used after surgery or radiation. It lowers the risk that the cancer will come back. It also reduces the risk of developing another breast cancer.

Treatments that can be used in hormone therapy include:

* Medicines that block hormones from attaching to cancer cells. These medicines are called selective estrogen receptor modulators. Examples include tamoxifen and raloxifene (Evista).
* Medicines that stop the body from making estrogen after menopause. These medicines are called aromatase inhibitors. Examples include anastrozole (Arimidex), exemestane (Aromasin) and letrozole (Femara).

Discuss the benefits and risks of hormone therapy with your healthcare team.

**Alternative medicine**

No alternative medicine treatments have been found to cure ductal carcinoma in situ, also called DCIS. But complementary and alternative medicine therapies may help you cope with side effects of treatment.

Combined with your healthcare team's recommendations, complementary and alternative medicine treatments may provide some comfort. Examples include:

* Art therapy.
* Exercise.
* Meditation.
* Music therapy.
* Relaxation exercises.
* Spirituality.

**Prevention**

Making changes in your daily life may help lower your risk of ductal carcinoma in situ. This early form of breast cancer also is called DCIS. To lower your risk of breast cancer, try to:

### **Ask about breast cancer screening**

Talk with your doctor or other healthcare professional about when to begin breast cancer screening. Ask about the benefits and risks of screening. Together, you can decide what breast cancer screening tests are right for you.

### **Become familiar with your breasts through breast self-exam for breast awareness**

You may choose to become familiar with your breasts by occasionally inspecting them during a breast self-exam for breast awareness. If you find a new change, lumps or other unusual signs in your breasts, tell a healthcare professional right away.

Breast awareness can't prevent breast cancer. But it may help you to better understand the look and feel of your breasts. This might make it more likely that you'll notice if something changes.

### **Drink alcohol in moderation, if at all**

If you choose to drink alcohol, limit the amount you drink to no more than one drink a day. For breast cancer prevention, there is no safe amount of alcohol. So if you're very concerned about your breast cancer risk, you may choose to not drink alcohol.

### **Exercise most days of the week**

Aim for at least 30 minutes of exercise on most days of the week. If you haven't been active lately, ask your healthcare professional whether exercising is OK and start slowly.

### **Limit hormone therapy during menopause**

Combination hormone therapy may increase the risk of breast cancer. Talk with a healthcare professional about the benefits and risks of hormone therapy.

Some people have symptoms during menopause that cause discomfort. These people may decide that the risks of hormone therapy are acceptable to get relief. To reduce the risk of breast cancer, use the lowest dose of hormone therapy possible for the shortest amount of time.

### **Maintain a healthy weight**

If your weight is healthy, work to maintain that weight. If you need to lose weight, ask a healthcare professional about healthy ways to lower your weight. Eat fewer calories and slowly increase the amount you exercise.

**QUESTION AND ANSWER SETS**

Do I have breast cancer?  
DCIS is a non-invasive or pre-invasive form of breast cancer. The abnormal cells are confined to the milk ducts and have not spread into surrounding breast tissue.

What tests do I need to determine the type and stage of cancer?  
Diagnosis typically involves a mammogram, possibly an ultrasound, and a biopsy to confirm DCIS. Additional imaging or tests may be used to rule out invasive cancer, but DCIS is considered stage 0 (non-invasive).

What treatment approach do you recommend?  
Standard treatment options include:

* Breast-conserving surgery (lumpectomy): Removes the DCIS and a margin of healthy tissue.
* Mastectomy: Removal of all breast tissue, considered if DCIS is widespread or in multiple areas.
* Radiation therapy: Often recommended after lumpectomy to reduce recurrence risk.
* Hormone therapy (e.g., tamoxifen): May be advised for hormone receptor-positive DCIS to reduce recurrence risk.

What are the possible side effects or complications of this treatment?

* Surgery: Pain, swelling, infection, changes in breast shape.
* Radiation: Fatigue, skin irritation, swelling, rare long-term effects.
* Hormone therapy: Hot flashes, fatigue, joint pain, increased risk of blood clots and, rarely, uterine cancer.

In general, how effective is this treatment?  
DCIS has an excellent prognosis. With current treatments, the 10-year breast cancer-specific survival rate is 97–98%. Most women with DCIS are cured with surgery (with or without radiation and/or hormone therapy).

Am I a candidate for tamoxifen?  
If your DCIS is hormone receptor-positive, tamoxifen or another hormone therapy may be recommended to reduce the risk of recurrence, especially if you are premenopausal or choose breast-conserving surgery. The decision depends on your personal risk factors and tolerance for side effects.

Am I at risk of this condition recurring?  
There is a risk of DCIS coming back, either as DCIS or as invasive cancer, particularly if you have breast-conserving surgery without radiation. Radiation and/or hormone therapy can lower this risk.

Am I at risk of developing invasive breast cancer?  
Yes, DCIS can recur as invasive cancer, but most cases do not progress if treated appropriately. The risk depends on tumor size, grade, margins, and treatment choices.

How will you treat DCIS if it returns?  
Recurrent DCIS or invasive cancer is usually treated with surgery (lumpectomy or mastectomy), possibly followed by radiation and/or hormone therapy, depending on the previous treatment and the nature of the recurrence.

How often will I need follow-up visits after I finish treatment?  
Follow-up typically includes a history and physical exam every 6–12 months for the first five years, then annually, with yearly mammograms. The first mammogram is usually 6–12 months after completing radiation.

What lifestyle changes can help reduce my risk of a DCIS recurrence?

* Maintain a healthy weight
* Exercise regularly
* Limit alcohol
* Avoid smoking
* Follow your treatment plan and attend all follow-up appointments

Do I need a second opinion?  
A second opinion can be helpful, especially if you are uncertain about your treatment plan or considering major surgery. Most providers support this.

Should I see a genetic counselor?  
Consider genetic counseling if you have a strong family history of breast or ovarian cancer, are diagnosed at a young age, or have other risk factors for hereditary breast cancer

**EPIDEMIOLOGY**

Overall, breast cancer is the most common cancer in women in the United States. In women aged 50 to 64 years of age, the risk of DCIS is as high as 88 per 100,000 women. Today, 20% to 25% of breast cancer diagnosed in the United States is DCIS. This has increased concurrently with screening mammography, as a significant percentage of DCIS is first identified on screening mammography. In the pre-screening mammography era, less than 5% of newly diagnosed breast cancers were DCIS. A recent 2020 NCI-funded study modeled the natural history of DCIS using a combination of 2 population models and 6 submodels. They found that 36% to 100% of DCIS progressed to invasive breast cancer without surgical excision or treatment, with a mean progression time of 0.2 to 2.5 years. DCIS overdiagnosis ranged from 3.1% to 65.8%. They concluded that the majority of DCIS would progress to invasive breast cancer. However, the wide variation has to do with the heterogeneity and subtype variation within DCIS, and more studies need to be done on various subtypes.

Other risk factors contribute to the progression of DCIS to invasive breast cancer. As a woman ages from birth to death, the probability of developing invasive breast cancer is 12.3% or 1 in 8.Increased exposure to estrogen can also increase the risk of developing breast cancer. The use of hormone replacement therapy in postmenopausal women has been associated with an increased risk of breast cancer. Additionally, a high endogenous level of estrogen increases the risk of breast cancer; this can be approximated by age at first menarche, age at menopause, and age at first live birth. Alcohol use is associated with an increased risk of breast cancer as well. Patients with first-degree relatives with breast cancer are at a higher risk of breast cancer.

## **Differential Diagnosis of Ductal Carcinoma In Situ (DCIS)**

## 1. Atypical Ductal Hyperplasia (ADH)

* Features: Shares architectural and cytological features with low-grade DCIS, but is less extensive.
* Key Point: If the atypical proliferation occupies two or more duct spaces, it is classified as low-grade DCIS; if less, it is ADH.
* Clinical Relevance: ADH is a risk marker, not cancer, but can be a precursor to DCIS.

## 2. Usual Ductal Hyperplasia

* Features: Heterogeneous proliferation of ductal cells with variable size and shape, irregular distribution, and haphazard nuclear orientation.
* Key Point: Lacks the uniformity, polarization, and architectural patterns of DCIS.
* Immunohistochemistry: Variable or mosaic pattern for CK5/6 and estrogen receptor.

## 3. Lobular Carcinoma In Situ (LCIS)

* Features: Low-grade, discohesive cells, often with a feathery clear space between cells and solid growth pattern.
* Key Point: LCIS cells lack polarization around luminal spaces and show loss of E-cadherin expression, unlike DCIS.

## 4. Invasive Carcinoma (e.g., Invasive Cribriform Carcinoma)

* Features: Infiltrative growth pattern with stromal reaction.
* Key Point: Invasive carcinoma lacks the intact myoepithelial cell layer that surrounds DCIS; myoepithelial markers (p40, p63, calponin, CK5/6) help distinguish.

## 5. Other Mimics

* Adenoid Cystic Carcinoma: Infiltrative, dual cell population, pseudo lumens with basement membrane material, positive for CD117/KIT and MYB, negative for hormone receptors.
* Collagenous Spherulosis: Pseudolumens with basement membrane nodules, surrounded by myoepithelial cells; lacks true cribriform spaces and is benign

## **Frequently Altered Genes and Regions**

* Common mutations in DCIS include:
  + *PIK3CA* (~24%)
  + *TP53* (~24%)
  + *AKT1*, *GATA3*, and *MAP3K1* (less frequently)
* Common chromosomal amplifications and gains:
  + 17q12 (*ERBB2/HER2* amplification; ~29%)
  + 17q21.1 (*GSDMB*, *PSMD3*)
  + 11q13 (*CCND1*)
  + 1q and 8p11 gains are more common in recurrent invasive disease.
* Loss of 3p21 is more common in primary DCIS and may represent subclones that do not progress to invasion.
* DNA hypermethylation of tumor suppressor genes is observed, suggesting epigenetic silencing plays a role in progression.

## 3. Clonal Relationships and Progression

* In about 75% of cases, invasive recurrences are clonally related to the initial DCIS, meaning they arise from the same ancestral cell and share most driver mutations and CNAs.
* There is no clear single genomic marker that predicts progression to invasion; rather, a combination of mutations and copy number changes, along with microenvironmental factors, likely determines which DCIS lesions become invasive.
* Pure DCIS can exhibit high genomic complexity, sometimes even more than DCIS associated with invasive carcinoma, but tends to be more genetically homogeneous

**doctor-patient conversation about ductal carcinoma in situ (DCIS)**

Doctor:  
Hello, thank you for coming in today. I have your biopsy results, and they show ductal carcinoma in situ, or DCIS.

Patient:  
Is DCIS breast cancer? How is it different from other types?

Doctor:  
DCIS is considered a non-invasive or pre-invasive form of breast cancer. The abnormal cells are confined to the milk ducts and haven’t spread into the surrounding breast tissue. This means it’s very treatable, and the prognosis is excellent.

Patient:  
What are my treatment options?

Doctor:  
Treatment usually involves surgery to remove the DCIS. For most people, that means a lumpectomy, which removes the abnormal area and a small margin of healthy tissue. Sometimes, a mastectomy is recommended if the DCIS is widespread. After surgery, radiation therapy may be advised to lower the risk of recurrence. If your DCIS is hormone receptor-positive, hormone therapy like tamoxifen may also be recommended.

Patient:  
What are the risks and side effects of these treatments?

Doctor:  
Surgery can cause pain, swelling, or changes in breast shape. Radiation therapy can lead to fatigue and skin irritation, and hormone therapy can cause hot flashes and other side effects. We’ll discuss each option in detail and tailor the plan to your needs.

Patient:  
What are my chances of DCIS coming back or turning into invasive cancer?

Doctor:  
With current treatments, the risk of DCIS returning or progressing to invasive cancer is low. The risk depends on factors like tumor size, grade, and your treatment choices. We use surgery, and sometimes radiation or hormone therapy, to keep these risks as low as possible.

Patient:  
Should I have genetic testing or see a genetic counselor?

Doctor:  
If you have a strong family history of breast or ovarian cancer, or if you were diagnosed at a young age, genetic counseling and testing might be helpful. It can inform your treatment and help assess your risk for other cancers.

Patient:  
How often will I need follow-up visits after treatment?

Doctor:  
After treatment, you’ll have checkups every 6–12 months for the first five years, then annually. You’ll also have yearly mammograms to monitor your breast health.

Patient:  
Are there lifestyle changes I can make to reduce my risk of recurrence?

Doctor:  
Yes. Maintaining a healthy weight, exercising regularly, limiting alcohol, not smoking, and keeping up with your follow-up care can all help reduce your risk.

Patient:  
Do I need to decide on treatment right away?

Doctor:  
While it’s important to address DCIS, you don’t need to rush your decision. Take time to consider your options, and let me know if you’d like a second opinion or more information.

REFERENCES

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[Ductal carcinoma in situ (DCIS) - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/dcis/diagnosis-treatment/drc-20371895)

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### **INVASIVE DUCTAL CARCINOMA**

**DEFINITION AND DESCRIPTION**

Invasive ductal carcinoma (IDC) accounts for about 80% of all breast cancer cases in females. It typically affects women age 55 and older. It’s also the most common male breast cancer. This article focuses on IDC affecting females.

Invasive ductal carcinoma starts in cells that line the milk ducts in your breast. It can spread from your milk duct to surrounding breast tissue. From there, the cancer can get into your bloodstream or lymphatic system and spread to other areas of your body.

Healthcare providers may use names like ductal carcinoma, infiltrating ductal carcinoma or IDC breast cancer when they talk about this condition. Often, healthcare providers can cure it if tests detect cancerous tumors before they spread to other areas of your body.

#### **Types of invasive ductal carcinoma**

IDC types reflect the tumors’ hormone receptor status. Receptors are protein molecules in or on cells’ surfaces. They can attract or attach to certain substances in your blood, including hormones like estrogen and progesterone that help cancerous tumors to grow. Knowing a breast cancer tumor’s hormone receptor status helps providers decide which treatment will be most effective.

Common types of invasive ductal carcinoma are:

* Triple-negative breast cancer.
* HER2-positive (HER2+) breast cancer.
* ER-positive (ER+) breast cancer.
* PR-positive (PR+) breast cancer.

## **Symptoms and Causes**

Often, routine mammograms detect invasive ductal carcinoma before you have noticeable symptoms. When IDC symptoms do appear, they may include:

* A change in the size, shape or contour of your breast.
* A mass or lump, which may feel as small as a pea.
* A lump or thickening in or near your breast or in your underarm that persists through your menstrual cycle.
* A change in the look or feel of your skin on your breast or nipple. Your skin may look dimpled, puckered, scaly or inflamed and reddened.
* A marble-like hardened area under your skin.
* A blood-stained or clear fluid discharge from your nipple.

### **What causes invasive ductal carcinoma?**

Experts don’t know the exact cause, but they believe the following activities or experiences may increase your risk of developing invasive ductal carcinoma:

* Smoking.
* Consuming beverages containing alcohol.
* Having obesity.
* Having had radiation therapy to your chest area.
* Starting your menstrual cycle earlier or later than usual.
* Having children later in life.

Certain inherited genetic mutations may increase your risk of developing invasive ductal carcinoma. An inherited genetic mutation is an abnormal gene or genes that you inherit from your biological parents.

### **Complications of this condition**

Invasive ductal carcinoma can spread (metastasize) to other areas of your body, including your liver, lungs, bones and brain.

## **Diagnosis and Tests**

A healthcare provider will perform a physical examination. They’ll check for lumps in your breasts. They may also check for swollen lymph nodes in your armpit. They may order other tests, including:

* Breast MRI.
* Breast ultrasound.
* Breast biopsy.

An oncologist and a cancer care team will use test results to plan your treatment. They do that by identifying the cancer stage and grade.

#### **Stages of IDC**

Healthcare providers base cancer stage on factors, like the tumor’s location and size. There are five stages of invasive ductal carcinoma:

* Stage 0: The cancer is localized to your milk ducts. This stage is also known as noninvasive ductal carcinoma in situ.
* Stage I (1): The cancer has spread outside of your milk ducts to your breast tissue, but it hasn’t spread to your lymph nodes. In some cases, cancer may be in your lymph nodes but not in surrounding breast tissue.
* Stage II (2): You have a small tumor that’s in one to three of your lymph nodes. A large tumor that hasn’t spread to lymph nodes is also a Stage II IDC.
* Stage III (3): There’s cancer in more than three of your lymph nodes. Cancer that causes breast skin inflammation is also a Stage III invasive ductal carcinoma.
* Stage IV (4): Invasive ductal carcinoma is in other organs like your liver, lungs, brain or chest wall. It may be in your bones or lymph nodes in more distant parts of your body.

#### **Grades of IDC**

Cancer cell grades are based on how much the cancerous cells look like normal cells when viewed under a microscope. When medical pathologists set cancer cell grades, they examine three parts, or aspects, of the cell and give each aspect or part a grade. Sometimes, pathologists use the terms “well-differentiated,” “moderately differentiated” or “poorly differentiated” instead of a number. The three grades are:

* Grade 1 (well-differentiated): The cancerous cells are growing slowly and look more like noncancerous breast cells.
* Grade 2 (moderately differentiated): The cells are growing faster than Grade 1 cells and look more like cancerous cells than noncancerous cells.
* Grade 3 (poorly differentiated): The cells look very different from noncancerous cells and are likely to grow and spread more quickly than Grade 1 and Grade 2 cells.

## **Management and Treatment**

Treatment options vary depending on your situation, including cancer stage and your personal preferences. IDC treatments may include:

* Breast cancer surgery: If you have surgery, it may be a lumpectomy or a mastectomy. Breast cancer surgery may involve breast reconstruction.
* Chemotherapy: Providers may do chemotherapy before surgery to shrink the tumor or after surgery to kill any remaining cancer cells that could be in your body. It may be your main treatment if you have metastatic (Stage IV) invasive ductal carcinoma.
* Radiation therapy: If you have surgery, you may have this treatment after to kill any remaining cancerous cells. This treatment may also be an option if surgery isn’t an option due to tumor size or location.
* Targeted therapy: This cancer treatment targets the genetic changes that turn healthy cells into cancerous cells.
* Hormone therapy: Cancer cells often need access to hormones to grow and multiply. Hormone therapy cuts off that access.
* Immunotherapy: Immunotherapy helps your immune system find and destroy cancerous cells.

#### **Treatment side effects**

Surgery is a common treatment for invasive ductal carcinoma. Pain after surgery is a common side effect. Providers may combine surgery with other treatments, too. Common chemotherapy and radiation therapy side effects include fatigue or nausea and vomiting.

Targeted therapy and immunotherapy have similar side effects like gastrointestinal issues, such as constipation and diarrhea. Hormone therapy side effects include hot flashes, joint pain and loss of interest in sex.

People react differently to breast cancer treatments. If you’re receiving treatment, ask your healthcare provider how treatment may affect you, including how it may affect your daily life. Ask your provider about palliative care, too. Palliative care helps manage breast cancer symptoms and treatment side effects so you’re as comfortable as possible as you go through treatment.

## **Outlook / Prognosis**

Survival rates for invasive ductal carcinoma are estimates based on the experiences of people who have it. The National Cancer Institute collects invasive ductal carcinoma rates by stages: local, regional and distant.

| **Stage** | **Survival rate** |
| --- | --- |
| Local (cancer hasn’t spread outside of your breast). | 100% |
| Regional (cancer has spread to nearby lymph nodes and tissue). | 86% |
| Distant (cancer is in more distant areas of your body like your liver or lungs). | 28% |

As you think about breast cancer survival rates, remember that they’re only estimates based on other people’s experiences. Cancer affects different people in different ways. If you have specific questions about cancer survival rates, talk to your healthcare provider. They’re your best resource because they know your situation.

## **Prevention**

No, it can’t, but you can take steps to reduce the chance you’ll develop invasive ductal carcinoma:

* Have regular mammograms. If you’re a female and have a family history of breast cancer, ask a healthcare provider if you should start having mammograms earlier than most people.
* Eat a well-balanced diet that helps you maintain a weight that’s right for you.
* Don’t smoke.
* Limit beverages containing alcohol to one drink a day.
* Exercise regularly.
* Talk to a healthcare provider about tests to detect genetic mutations that increase your risk of developing breast cancer.

## **Living With**

Living with invasive ductal carcinoma (IDC) may not be easy. You may have days when you feel overwhelmed by your situation. Consider the following suggestions for taking care of yourself as you go through diagnosis and treatment for IDC:

* Get enough rest. IDC and treatment can be exhausting. Try to remember to rest when you need to, not just when you can.
* Eat well. Treatment may affect your appetite. A diet of fruit, vegetables, lean protein and healthy grains can help you stay strong during treatment.
* Manage your stress. Cancer is stressful. Exercise can help, from regular walks to exercise programs.
* Find support. You’re a breast cancer survivor starting the day you receive your diagnosis. Ask your healthcare provider about cancer survivorship programs, which may help you manage some of the challenges that come with living with IDC.

### **When should I see my healthcare provider?**

Contact your provider if you have symptoms that may be signs that invasive ductal carcinoma is spreading from your milk ducts to your breast tissue, to nearby lymph nodes or other areas of your body. Metastatic IDC symptoms may include:

* New lumps in your breast.
* Swollen lymph nodes in your armpit.
* Chest pain.
* Shortness of breath (dyspnea).
* Bone pain.
* Belly pain.
* Confusion.

Go to the ER if you’re receiving treatment and have side effects that are more intense than you anticipated. You should also go to the ER if you have chills or a fever that’s 104 degrees Fahrenheit (38 degrees Celsius) or higher. A high fever and chills may be symptoms of infection.

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## **Common Questions**

### **What is the most aggressive form of breast cancer?**

The most aggressive form of breast cancer is metastatic breast cancer. This means that the cancer has spread from your breast tissue to distant areas of your body.

### **What is triple-negative invasive ductal carcinoma?**

Triple-negative breast cancer makes up about 15% of all breast cancers. In these cases, the cancer cells don’t have estrogen or progesterone receptors. They also don’t make much of the HER2 protein. Triple-negative invasive ductal carcinomas grow and spread faster than other types of breast cancer. The main treatment for this type of breast cancer is chemotherapy. Immunotherapy is added to chemotherapy for certain patients with this type of breast cancer.

### **Is invasive breast cancer aggressive?**

Invasive breast cancer, such as invasive ductal carcinoma, tends to be more aggressive than non-invasive breast cancer (ductal carcinoma in situ, DCIS). However, the level of aggressiveness depends on the type, stage, prognostic factors, and grade of invasive breast cancer.

Generally, triple-negative breast cancer and inflammatory breast cancer tend to be the most aggressive types of invasive breast cancer because they are faster growing and harder to treat than some other types. Grade 3 breast cancer also tends to be more aggressive than other grades.

### **Is invasive ductal carcinoma curable?**

Many healthcare professionals no longer use the word “cured” when referring to the end of breast cancer treatment. Instead, they will often refer to the patient as “cancer-free.” With vigilant treatment and support, many individuals diagnosed with invasive ductal carcinoma are declared cancer-free at the end of treatment.

### **How long can you live with invasive ductal carcinoma?**

The length of time a person can live with invasive ductal carcinoma depends on the type and stage of the cancer at diagnosis. When detected and treated early, the prognosis and life expectancy for those with IDC is very good, and many may expect to live an equally long life as someone who never experienced invasive ductal carcinoma.

### **Is invasive ductal carcinoma hereditary?**

Invasive ductal carcinoma and other types of breast cancer may be hereditary (or genetic) in 5-10% of cases. While the type of breast cancer passed through the genes is not hereditary, it is statistically more likely to be IDC since it is the most common form of breast cancer. This means that in 5-10% of breast cancer cases, a breast cancer gene mutation was passed down from a parent to a child. Individuals with an inherited BRCA gene mutation or other breast cancer gene mutation have a 45-65% chance of developing breast cancer in their lifetime.

### **Can invasive ductal carcinoma spread?**

Yes. IDC is called “invasive” breast cancer because it can spread—or invade—healthy breast tissue, lymph nodes, or into other organs of the body, increasing the stage of IDC. Invasive ductal carcinoma is most treatable when it is caught and treated early before it has a chance to spread.

### **Does invasive ductal carcinoma return?**

Even after successful treatment, IDC can return in the form of a breast cancer recurrence. There are different types of recurrence. A local recurrence is when cancer returns at or near the original location in the breast; a regional recurrence is when cancer returns in the lymph nodes near the original site of the cancer; and a distant recurrence is when breast cancer cells reappear in distant areas of the body, such as the bones, liver, lungs, or brain. A distant recurrence of invasive ductal carcinoma is called metastatic breast cancer.

**EPIDEMIOLOGY**

Prevalence and Incidence

* IDC is the most common type of breast cancer, accounting for about 80% of all breast cancer diagnoses in women and nearly all breast cancers in men.
* In 2025, an estimated 319,750 new cases of invasive breast cancer (predominantly IDC) will be diagnosed in the United States.
* Globally, breast cancer (of which IDC is the major subtype) affected 2.3 million women in 2022.

Demographics

* IDC is much more common in females, but about 98% of male breast cancers are IDC.
* Most cases occur in women older than 50 years.
* White women in the US have higher incidence rates than Black or Hispanic women; however, Black and Hispanic women often develop more aggressive forms at a younger age.
* The mean age at diagnosis is around 60 years, but cases span from age 30 to over 80.

Trends

* Incidence rates of IDC have increased over the past 20 years, likely due to improved screening and early detection.
* Advances in screening and treatment have led to lower mortality rates in recent decades.

Staging and Tumor Characteristics

* The most common tumor sizes at diagnosis are T1c (1–2 cm) and T2 (2–5 cm).
* More than half of IDC cases are histologic grade 2 (moderate differentiation), with a significant proportion being grade 3 (poorly differentiated).
* At diagnosis, about 45% of IDC cases have no lymph node involvement, but risk increases with higher tumor grade and size.

Survival

* 5-year relative survival rates for IDC (all stages combined) are about 91% in the US.
  + Localized (confined to breast): 99%
  + Regional (spread to nearby lymph nodes): 87%
  + Distant (metastasized): 32%

## **Differential Diagnosis of Invasive Ductal Carcinoma (IDC)**

## Benign Conditions

* Fibroadenoma: Benign, mobile breast mass; usually well-circumscribed on imaging and lacks malignant histology.
* Fibrocystic changes: May present as lumpy, tender breasts; imaging and biopsy distinguish from IDC.
* Intraductal papilloma: Benign tumor within a duct; can cause nipple discharge and may show a mass on imaging.
* Sclerosing adenosis: Proliferation of lobules that can mimic carcinoma on imaging and histology.
* Fat necrosis: Firm, irregular mass often after trauma or surgery; may mimic IDC on imaging but has characteristic histology.
* Radial scar: Benign lesion with stellate appearance on imaging; requires biopsy to rule out carcinoma.

## Other Malignant and Premalignant Conditions

* Ductal carcinoma in situ (DCIS): Non-invasive cancer confined to ducts; lacks invasion into surrounding tissue, unlike IDC.
* Invasive lobular carcinoma: Malignant tumor with different growth pattern; often more diffuse and harder to detect on imaging.
* Mucinous carcinoma: Malignant, but with mucin-producing cells; generally has a better prognosis.
* Lobular carcinoma in situ (LCIS): Non-invasive, marker of increased risk, not a true cancer.

## Other Systemic or Inflammatory Conditions

* Mastitis or breast abscess: Infection or inflammation, can mimic inflammatory breast cancer; clinical history and response to antibiotics help differentiate.
* Plasma cell mastitis: Chronic inflammation that may mimic IDC on imaging; MRI and histology are helpful for distinction.
* Autoimmune disorders (e.g., lupus): May cause breast changes that mimic malignancy

## **Common Genomic Alterations in IDC**

* Frequently Mutated Genes:
  + *PIK3CA* (24–27%)
  + *TP53* (24–27%)
  + *GATA3* (up to 19% in some DCIS cohorts, associated with relapse risk)
* Common Copy Number Gains:
  + 17q12 (*ERBB2/HER2* amplification, ~27–29%)
  + 17q21.1 (*GSDMB*, *PSMD3*)
  + 11q13 (*CCND1*)
  + Gains on 1q and 8p11 are more common in recurrent invasive disease.
* Common Copy Number Losses:
  + 3p21 loss is more frequent in primary DCIS and may represent subclones that do not progress to invasion.

**Doctor-patient conversation about invasive ductal carcinoma (IDC),**

Doctor:  
Thank you for coming in today. I have your test results, and they show that you have invasive ductal carcinoma, or IDC. This means the cancer started in the milk ducts of your breast and has spread into the surrounding breast tissue.

Patient:  
What does that mean for me? How serious is it?

Doctor:  
IDC is the most common type of breast cancer. The seriousness depends on several factors, including the size and location of the tumor, whether it has spread to lymph nodes or other parts of the body, and the specific characteristics of the cancer cells, like their grade and hormone receptor status.

Patient:  
What are my treatment options?

Doctor:  
Treatment is tailored to your situation. Most people have surgery—either a lumpectomy, which removes just the tumor, or a mastectomy, which removes the whole breast. We may also recommend radiation therapy, chemotherapy, hormone therapy, or targeted therapy, depending on your cancer’s stage and biology. For example, if your tumor is hormone receptor-positive, hormone therapy can help lower the risk of recurrence.

Patient:  
What side effects should I expect?

Doctor:  
Side effects depend on the treatments you receive. After surgery, you may have pain or changes in breast appearance. Radiation can cause fatigue and skin irritation. Chemotherapy may cause nausea, fatigue, and hair loss. Hormone therapy can lead to hot flashes and joint pain. Targeted therapies and immunotherapies may cause gastrointestinal symptoms or, rarely, effects on the heart. We’ll discuss ways to manage these side effects and keep you as comfortable as possible.

Patient:  
How will treatment affect my daily life?

Doctor:  
Most people can continue many of their normal activities, but you may need to adjust your schedule, especially during chemotherapy or radiation. Fatigue is common, and you may need extra rest. It’s important to communicate with us about how you’re feeling so we can support you.

Patient:  
What’s the outlook?

Doctor:  
The prognosis for IDC is generally very good, especially when detected early. With appropriate treatment, most people do very well. Your specific outlook depends on your cancer’s stage, grade, and other factors, which we’ll discuss in detail.

Patient:  
What happens next?

Doctor:  
We’ll work together to develop a treatment plan that’s right for you. I’ll answer all your questions and connect you with our support team, including nurses, counselors, and nutritionists, to help you through every step.

REFERENCES

<https://www.breastcancer.org/types/invasive-ductal-carcinoma>

<https://www.hopkinsmedicine.org/health/conditions-and-diseases/breast-cancer/invasive-ductal-carcinoma-idc>

[Invasive Ductal Carcinoma (IDC): Stages & Treatment](https://my.clevelandclinic.org/health/diseases/22117-invasive-ductal-carcinoma-idc#overview)

**INVASIVE LOBULAR CARCINOMA**

**DEFINITION AND DESCRIPTION**

Invasive lobular carcinoma is a type of breast cancer that begins as a growth of cells in the milk-producing glands of the breast. These glands are called lobules.

Invasive cancer means that the cancer cells have broken out of the lobule where they began and spread into the breast tissue. The cells have the potential to spread to the lymph nodes and other areas of the body.

Invasive lobular carcinoma makes up a small portion of all breast cancers. The most common type of breast cancer begins in the breast ducts. This type is called invasive ductal carcinoma.

**Risk factors**

Risk factors for invasive lobular carcinoma are thought to be similar to the risk factors for breast cancer in general. Factors that may increase the risk of breast cancer include:

* **A family history of breast cancer.** If a parent, sibling or child had breast cancer, your risk of breast cancer is increased. The risk is higher if your family has a history of getting breast cancer at a young age. The risk also is higher if you have multiple family members with breast cancer. Still, most people diagnosed with breast cancer don't have a family history of the disease.
* **A personal history of breast cancer.** If you've had cancer in one breast, you have an increased risk of getting cancer in the other breast.
* **A personal history of breast conditions.** Certain breast conditions are signs that you have a higher risk of breast cancer. These conditions include lobular carcinoma in situ, also called LCIS, and atypical hyperplasia of the breast. If you've had a breast biopsy that found one of these conditions, you have an increased risk of breast cancer.
* **Beginning your period at a younger age.** Beginning your period before age 12 increases your risk of breast cancer.
* **Beginning menopause at an older age.** Beginning menopause after age 55 increases the risk of breast cancer.
* **Being female.** Women are much more likely than men are to get breast cancer. Everyone is born with some breast tissue, so anyone can get breast cancer.
* **Dense breast tissue.** Breast tissue is made up of fatty tissue and dense tissue. Dense tissue is made of milk glands, milk ducts and fibrous tissue. If you have dense breasts, you have more dense tissue than fatty tissue in your breasts. Having dense breasts can make it harder to detect breast cancer on a mammogram. If a mammogram showed that you have dense breasts, your risk of breast cancer is increased. Talk with your healthcare team about other tests you might have in addition to mammograms to look for breast cancer.
* **Drinking alcohol.** Drinking alcohol increases the risk of breast cancer.
* **Having your first child at an older age.** Giving birth to your first child after age 30 may increase the risk of breast cancer.
* **Having never been pregnant.** Having been pregnant one or more times lowers the risk of breast cancer. Never having been pregnant increases the risk.
* **Inherited DNA changes that increase cancer risk.** Certain DNA changes that increase the risk of breast cancer can be passed from parents to children. Two DNA changes associated with an increased risk of invasive lobular carcinoma include BRCA2 and CDH1. BRCA2 increases the risk of breast cancer and ovarian cancer. CDH1 increases the risk of breast cancer and stomach cancer. CDH1 is closely associated with a rare inherited condition called hereditary diffuse gastric cancer syndrome.
* **Menopausal hormone therapy.** Taking certain hormone therapy medicines to control the symptoms of menopause may increase the risk of breast cancer. The risk is linked to hormone therapy medicines that combine estrogen and progesterone. The risk goes down when you stop taking these medicines.
* **Obesity.** People with obesity have an increased risk of breast cancer.
* **Older age.** Your risk of breast cancer increases as you age. Invasive lobular carcinoma tends to happen at an older age compared to other types of breast cancer.
* **Radiation exposure.** If you received radiation treatments to your chest as a child or young adult, your risk of breast cancer is higher.

## **Symptoms and Causes**

Most of the time, breast cancer happens when cancer cells multiply to create a tumor. The tumor may make a lump in your breast that you can feel. ILC is different. Early on, ILC cells spread out in a single file to form strands or strings of cancer cells.

As ILC grows slowly and may not form a lump, it may not cause noticeable changes in your breasts. When it does, symptoms can include:

* Breast pain or warmth
* Breast skin that looks or feels thicker than usual or has dimples, tiny dents or puckers
* Changes in breast size and shape, like an area of swelling or fullness
* Inverted nipple that points into your breast instead of pointing out
* Lump near your armpit
* Nipple discharge
* Skin discoloration that appears reddish or darker than usual

### **Invasive lobular cancer causes**

ILC happens when genetic mutations (changes) turn healthy cells into cancer cells. Experts aren’t sure what causes the mutations. Researchers believe the following factors increase your risk of having invasive lobular carcinoma:

* Being age 55 and older
* Giving birth after age 30 or not giving birth
* Having had breast cancer previously
* Having a family history of breast cancer or ovarian cancer
* Having lobular carcinoma in situ (LCIS)
* Inheriting certain genetic mutations
* Starting menopause later than usual (after age 55)
* Starting your period earlier than usual (before age 12)
* Receiving certain types of hormone therapy for menopause symptoms

## **Diagnosis and Tests**

A healthcare provider will ask about your symptoms. They’ll examine your breasts and the area near your armpits. They may do the following tests:

* Mammogram to look for abnormal masses or changes in your breasts

A mammogram is an X-ray of the breast tissue. Mammograms are commonly used to screen for breast cancer. If a screening mammogram finds something concerning, you might have another mammogram to look at the area more closely. This more-detailed mammogram is called a diagnostic mammogram. It's often used to look closely at both breasts. Invasive lobular carcinoma is less likely to be detected on a mammogram than other types of breast cancer are. Still, a mammogram is a useful diagnostic test.

* Breast MRI to get very detailed images of your breast tissue

MRI machines use a magnetic field and radio waves to create pictures of the inside of the body. A breast MRI can make more-detailed pictures of the breast. Sometimes this method is used to look closely for any other areas of cancer in the affected breast. It also might be used to look for cancer in the other breast. Before a breast MRI, you usually receive an injection of dye. The dye helps the tissue show up better in the images.

* Breast ultrasound to focus on specific areas of your breasts

Ultrasound uses sound waves to make pictures of structures inside the body. A breast ultrasound may give your healthcare team more information about a breast lump. For example, an ultrasound might show whether the lump is a solid mass or a fluid-filled cyst. The healthcare team uses this information to decide what tests you might need next. Invasive lobular carcinoma may be more difficult to detect with ultrasound than other types of breast cancer.

During a clinical breast exam, a healthcare professional looks at the breasts for anything that's not typical. This might include changes in the skin or to the nipple. Then the health professional feels the breasts for lumps. The health professional also feels along the collarbones and around the armpits for lumps

They may recommend a breast biopsy to get a small sample of your breast tissue. A medical pathologist will examine the tissue under a microscope. They’ll look for abnormal breast cells and other cancer signs.

A biopsy is a procedure to remove a sample of tissue for testing in a lab. To get the sample, a healthcare professional often puts a needle through the skin and into the breast tissue. The health professional guides the needle using images created with X-rays, ultrasound or another type of imaging. Once the needle reaches the right place, the health professional uses the needle to draw out tissue from the breast. Often, a marker is placed in the spot where the tissue sample was removed. The small metal marker will show up on imaging tests. The marker helps your healthcare team monitor the area of concern.

### **Testing cells in the lab**

The tissue sample from a biopsy goes to a lab for testing. Tests can show whether the cells in the sample are cancerous. Other tests give information about the type of cancer and how quickly it's growing. The results of these tests tell your healthcare team if you have invasive lobular carcinoma.

Special tests give more details about the cancer cells. For example, tests might look for hormone receptors on the surface of the cells. Your healthcare team uses the results from these tests to make a treatment plan.

### **Staging breast cancer**

Once your healthcare team diagnoses your invasive lobular carcinoma, you may have other tests to figure out the extent of the cancer. This is called the cancer's stage. Your healthcare team uses your cancer's stage to understand your prognosis.

Complete information about your cancer's stage may not be available until after you have breast cancer surgery.

Tests and procedures used to stage invasive lobular carcinoma may include:

* Blood tests, such as a complete blood count and tests to show how well the kidneys and liver are working.
* Bone scan.
* CT scan.
* MRI.
* Positron emission tomography scan, also called a PET scan.

Not everyone needs all of these tests. Your healthcare team picks the right tests based on your specific situation.

The stages of invasive lobular carcinoma are the same as the stages for other types of breast cancer. Breast cancer stages range from 0 to 4. A lower number means the cancer is less advanced and more likely to be cured. Stage 0 breast cancer is cancer that is contained within a breast duct. It hasn't broken out to invade the breast tissue yet. As the cancer grows into the breast tissue and gets more advanced, the stages get higher. A stage 4 breast cancer means that the cancer has spread to other parts of the body.

Your cancer care team will use test results to stage the cancer and plan your treatment. There are four stages of invasive lobular carcinoma:

* Stage I is a tumor that measures up to 2 centimeters (cm) (about 3/4-inch) across and may be in nearby lymph nodes.
* Stage II means the tumor is 2 cm and is spreading to nearby lymph nodes. This stage also includes tumors that measure 5 cm or more (2 inches) across but haven’t spread into lymph nodes.
* Stage III means there’s cancer in your breast and lymph nodes. There are more lymph nodes with cancer than there are if you have stage II cancer.
* Stage IV is cancer that has spread to distant areas of your body, such as your lungs, liver or bones.

## **Management and Treatment**

Your treatment may be a combination of:

* Breast cancer surgery

Surgery for invasive lobular carcinoma typically involves a procedure to remove the breast cancer and a procedure to remove some nearby lymph nodes. Options include:

* **Removing breast cancer.** A lumpectomy is surgery to remove the invasive lobular carcinoma and some of the healthy tissue around it. The rest of the breast tissue isn't removed. Other names for this surgery are breast-conserving surgery and wide local excision. Most people who have a lumpectomy also have radiation therapy.  
  Lumpectomy might be used to remove a small cancer. Sometimes you can have chemotherapy before surgery to shrink the cancer so that lumpectomy is possible.
* **Removing all of the breast tissue.** A mastectomy is surgery to remove all breast tissue from a breast. The most common mastectomy procedure is total mastectomy, also called simple mastectomy. This procedure removes nearly all of the breast, including the lobules, ducts, fatty tissue and some skin, including the nipple and areola.  
  Mastectomy might be used to remove a large invasive lobular carcinoma. It also might be needed when there are multiple areas of cancer within one breast. You might have a mastectomy if you can't have or don't want radiation therapy after surgery.  
  Some newer types of mastectomy procedures might not remove the skin or nipple. For instance, a skin-sparing mastectomy leaves some skin. A nipple-sparing mastectomy leaves the nipple and the skin around it, called the areola. These newer operations can improve the look of the breast after surgery, but they aren't options for everyone.
* **Removing a few lymph nodes.** A sentinel node biopsy is an operation to take out some lymph nodes for testing. When invasive lobular carcinoma and other types of breast cancer spread, they often go to the nearby lymph nodes first. To see if the cancer has spread, a surgeon removes some of the lymph nodes near the cancer. If no cancer is found in those lymph nodes, the chance of finding cancer in any of the other lymph nodes is small. No other lymph nodes need to be removed.
* **Removing several lymph nodes.** Axillary lymph node dissection is an operation to remove many lymph nodes from the armpit. Your breast cancer surgery might include this operation if imaging tests show the cancer has spread to the lymph nodes. It also might be used if cancer is found in a sentinel node biopsy.
* **Removing both breasts.** Some people who have invasive lobular carcinoma in one breast may choose to have their other breast removed, even if it doesn't have cancer. This procedure is called a contralateral prophylactic mastectomy or a risk-reducing mastectomy. It might be an option if you have a high risk of getting cancer in the other breast. The risk might be high if you have a strong family history of cancer or have DNA changes that increase the risk of cancer. Most people with breast cancer in one breast will never get cancer in the other breast.

Complications of breast cancer surgery depend on the procedures you choose. All operations have a risk of pain, bleeding and infection. Removing lymph nodes in the armpit carries a risk of arm swelling, called lymphedema.

You may choose to have breast reconstruction after mastectomy surgery. Breast reconstruction is surgery to restore shape to the breast. Options might include reconstruction with a breast implant or reconstruction using your own tissue. Consider asking your healthcare team for a referral to a plastic surgeon before your breast cancer surgery.

* Chemotherapy before or after surgery

Chemotherapy treats cancer with strong medicines. Many chemotherapy medicines exist. Treatment often involves a combination of chemotherapy medicines. Most are given through a vein. Some are available in pill form.

Chemotherapy for invasive lobular carcinoma and other types of breast cancer is often used after surgery. It can kill any cancer cells that might remain and lower the risk of the cancer coming back.

Sometimes chemotherapy is given before surgery for invasive lobular carcinoma and other types of breast cancer. The chemotherapy might shrink the breast cancer so that it's easier to remove. Chemotherapy before surgery also might control cancer that spreads to the lymph nodes. If the lymph nodes no longer show signs of cancer after chemotherapy, surgery to remove many lymph nodes might not be needed. How the cancer responds to chemotherapy before surgery helps the healthcare team make decisions about what treatments might be needed after surgery.

When the cancer spreads to other parts of the body, chemotherapy can help control it. Chemotherapy may relieve symptoms of advanced cancer, such as pain.

Chemotherapy side effects depend on which medicines you receive. Common side effects include hair loss, nausea, vomiting, feeling very tired and having an increased risk of getting an infection. Rare side effects can include premature menopause and nerve damage. Very rarely, certain chemotherapy medicines can cause blood cell cancer.

* Hormone therapy if tests show you have estrogen receptor-positive (ER+) breast cancer

Hormone therapy, also called endocrine therapy, uses medicines to block certain hormones in the body. It's a treatment for breast cancers that are sensitive to the hormones estrogen and progesterone. Healthcare professionals call these cancers estrogen receptor positive and progesterone receptor positive. Cancers that are sensitive to hormones use the hormones as fuel for their growth. Blocking the hormones can cause the cancer cells to shrink or die. Most invasive lobular carcinomas are sensitive to hormones, so they are likely to respond to this treatment.

Hormone therapy is often used after surgery and other treatments. It can lower the risk that the cancer will come back.

If the invasive lobular carcinoma spreads to other parts of the body, hormone therapy can help control it.

Treatments that can be used in hormone therapy include:

* Medicines that block hormones from attaching to cancer cells. These medicines are called selective estrogen receptor modulators.
* Medicines that stop the body from making estrogen after menopause. These medicines are called aromatase inhibitors.
* Surgery or medicines to stop the ovaries from making hormones.

Sometimes hormone therapy medicines are combined with targeted therapy medicines. This combination can make hormone therapy more effective.

Hormone therapy side effects depend on the treatment you receive. The side effects can include hot flashes, night sweats and vaginal dryness. More-serious side effects include a risk of bone thinning and blood clots.

* Radiation therapy to kill any cancer cells that may remain after surgery

Radiation therapy treats cancer with powerful energy beams. The energy can come from X-rays, protons or other sources.

The radiation used to treat invasive lobular carcinoma and other types of breast cancer is often external beam radiation. During this type of radiation therapy, you lie on a table while a machine moves around you. The machine directs radiation to precise points on your body. Less often, the radiation can be placed inside the body. This type of radiation is called brachytherapy.

Radiation therapy is often used after surgery. It can kill any cancer cells that might be left after surgery. The radiation lowers the risk of the cancer coming back.

Side effects of radiation therapy include feeling very tired and having a sunburn-like rash where the radiation is aimed. Breast tissue also may look swollen or feel more firm. Rarely, more-serious side effects can happen. These include damage to the heart or lungs. Very rarely, a new cancer can grow in the treated area.

* Targeted therapy focuses on genetic mutations that turn healthy cells into cancer cells

Targeted therapy uses medicines that attack specific chemicals in the cancer cells. By blocking these chemicals, targeted treatments can cause cancer cells to die.

The most common targeted therapy medicines for breast cancer target the protein HER2. Some breast cancer cells make extra HER2. This protein helps the cancer cells grow and survive. Targeted therapy medicine attacks the cells that are making extra HER2 and doesn't hurt healthy cells. Most invasive lobular carcinomas don't make extra HER2, so they are unlikely to respond to treatments that target HER2.

Many other targeted therapy medicines exist for treating breast cancer. Your cancer cells may be tested to see whether these medicines might help you.

Targeted therapy medicines can be used before surgery to shrink a breast cancer and make it easier to remove. Some are used after surgery to lower the risk that the cancer will come back. Others are used only when the cancer has spread to other parts of the body.

#### **Recovery time**

Your recovery will depend on your treatment. For example, it can take two to four weeks to recover from breast cancer surgery. Recovering from treatments like chemotherapy may take six months to a year. It’s important to understand how cancer treatment may affect your daily routine. Don’t hesitate to ask your oncologists what to expect in terms of recovery.

**Alternative medicine**

No alternative medicine treatments have been found to cure invasive lobular carcinoma or other types of breast cancer. But complementary and alternative medicine therapies may help you cope with the side effects of treatment.

### **Alternative treatments for hot flashes**

Hot flashes are bouts of sudden, intense warmness that can leave you sweaty and uncomfortable. They can be a symptom of natural menopause or a side effect of hormone therapy for breast cancer. Hormone therapy, also called endocrine therapy, is often used to treat invasive lobular carcinoma.

Talk to your healthcare professional if you experience hot flashes. Many conventional treatments are available for hot flashes, including medicines.

If treatments for hot flashes don't work as well as you'd like, it might help to add complementary and alternative treatments to help you feel better.

Options might include:

* Acupuncture.
* Hypnosis.
* Meditation.
* Relaxation techniques.
* Tai chi.
* Yoga.

While none of these alternative treatments are proved to help control hot flashes, evidence shows that some breast cancer survivors find them helpful.

If you're interested in trying alternative treatments for hot flashes, talk to your healthcare team about your options.

### **When should I see my cancer care team?**

Contact your cancer care team if you have:

* Surgical wound infection symptoms like a fever (greater than 101 degrees Fahrenheit or 38.4 degrees Celsius) or thick, cloudy discharge from the incision (cut)
* Cancer treatment side effects that are stronger than you expected, like vomiting that you can’t control
* Pain that prescription pain medication doesn’t ease

## **Outlook / Prognosis**

Cancer survival rates are estimates of the percentage of people with a specific cancer diagnosis who are alive after a certain time — usually one to five years — after they receive a diagnosis.

Research shows that overall, 94% of women with ILC were alive and cancer-free five years after their diagnosis. That estimate includes women who have stage I to stage III when they’re diagnosed. In general, the earlier the stage at diagnosis, the better the prognosis. About 86% of women with ILC are alive and cancer-free 10 years after their diagnosis.

The five-year survival rates for ILC are similar to other types of breast cancer. But they’re 4% to 10% lower at that 10-year mark.

Healthcare providers are working to understand why this is and come up with treatment options to improve your chances of being cancer-free in the long run.

The rates don’t predict how long you’ll live with cancer. Survival rate information can be confusing and cause concern. If you have questions, your oncologist will explain what a survival rate means in your situation.

**Prevention**

Making changes in your daily life may help lower your risk of invasive lobular carcinoma and other types of breast cancer. Try to:

### **Ask about breast cancer screening**

Talk with your doctor or other healthcare professional about when to begin breast cancer screening. Ask about the benefits and risks of screening. Together, you can decide what breast cancer screening tests are right for you.

### **Become familiar with your breasts through breast self-exam**

You may choose to become familiar with your breasts by occasionally inspecting them during a breast self-exam for breast awareness. If there is a new change, a lump or something not typical in your breasts, report it to a healthcare professional right away.

Breast awareness can't prevent breast cancer. But it may help you to better understand the look and feel of your breasts. This might make it more likely that you'll notice if something changes.

### **Drink alcohol in moderation, if at all**

If you choose to drink alcohol, limit the amount you drink to no more than one drink a day. For breast cancer prevention, there is no safe amount of alcohol. So if you're very concerned about your breast cancer risk, you may choose to not drink alcohol.

### **Exercise most days of the week**

Aim for at least 30 minutes of exercise on most days of the week. If you haven't been active lately, ask a healthcare professional whether it's OK and start slowly.

### **Limit menopausal hormone therapy**

Combination hormone therapy may increase the risk of breast cancer. Talk with a healthcare professional about the benefits and risks of hormone therapy.

Some people have symptoms during menopause that cause discomfort. These people may decide that the risks of hormone therapy are acceptable in order to get relief. To reduce the risk of breast cancer, use the lowest dose of hormone therapy possible for the shortest amount of time.

### **Maintain a healthy weight**

If your weight is healthy, work to maintain that weight. If you need to lose weight, ask a healthcare professional about healthy ways to lower your weight. Eat fewer calories and slowly increase the amount of exercise.

### **Talk with a healthcare professional about your cancer risk**

If you have a family history of breast cancer or feel that you may have an increased risk of breast cancer, talk about it with your healthcare professional. Preventive medicines, surgery and more-frequent screening may be options for people with a high risk of breast cancer.

## **Subtypes of invasive lobular carcinoma**

There are several subtypes of invasive lobular carcinoma. Subtypes of ILC are assigned based on how the cancerous cells look under a microscope. All subtypes of ILC are usually cared for and treated the same way.

Invasive lobular carcinoma subtypes include:

* Classic ILC: The most common subtype, classic ILC refers to small cancer cells that have invaded the stroma, or the connective tissue that surrounds the breast ducts and lobules.
* Solid ILC: Solid ILC cells grow in large sheets with little connective tissue (stroma) between them.
* Alveolar ILC: A very rare subtype, alveolar ILC is characterized by clusters of ILC cells rather than the usual single-file lines.
* Tubulolobular ILC: This type of ILC is a combination of some cells that grow in single-file lines and others that form hollow tube-like structures.
* Pleomorphic ILC: A very rare subtype, pleomorphic ILC is characterized by larger cancerous cells with distinctly different centers (nuclei) than other subtypes of ILC.

### **Invasive lobular carcinoma recurrence**

Invasive lobular carcinoma recurrence is when the cancer is later found to still be present in the body somewhere after initial successful treatment. Recurrence can be local (within the remaining breast tissue) regional (in the lymph nodes under the arm or near the clavicle bone), or a distant, with breast cancer cells appearing in other organs of the body. If ILC returns as a distant recurrence, it commonly reappears in the colon, uterus, ovaries, and stomach.

It’s important to keep in mind that every individual and every cancer is unique. There is no statistic that can accurately predict the chances of a breast cancer recurrence. Hormone receptor-positive (HR+) breast cancers, such as most ILC, tend to have a lower rate of recurrence in the first 5 years after diagnosis than hormone receptor-negative (HR-) breast cancers. However, HR+ breast cancers can recur at a higher rate than HR- cancers 10+ years after treatment.

A recurrence of invasive lobular carcinoma cannot be prevented, but there are ways to lower the risk of recurrence, including:

* Staying in contact with your oncologist for follow-up appointments
* Taking hormonal therapy exactly as prescribed (if cancer was hormone receptor-positive)
* Continuing early detection (mammograms and breast self-exams) on any remaining breast tissue, as recommended by your doctor
* Eating well to ensure proper nutrition
* Maintaining a healthy weight
* Participating in regular physical activity or exercise
* Not smoking or drinking alcohol

## **Epidemiology:**

Invasive lobular carcinoma (ILC) is the second most common invasive breast cancer accounting for 5-15% of invasive breast cancers behind invasive ductal carcinoma (IDC). ILC is typically seen in post-menopausal women, peaking at age 50-60. It is more common in white individuals but has a higher mortality rate in African American individuals as they have a higher predisposition to have grade 3 ILC. Additionally, with the increased rate of post-menopausal hormone therapy, the incidence of ILC has increased over the last 20 years.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnoses of invasive lobular carcinoma include both carcinomatous and non-carcinomatous neoplasms :

* Invasive ductal carcinoma with lobular features
* Gastric signet ring carcinoma metastatic to the breast
* Sclerosing epithelioid fibrosarcoma
* Leukemic and lymphomatous involvement of the breast
* Rosai-Dorfman disease
* Granular cell tumor

## **Doctor-Patient Conversation: Invasive Lobular Carcinoma**

Doctor: Thank you for coming in today. I understand you recently had a biopsy, and I’d like to discuss your results. You have a type of breast cancer called invasive lobular carcinoma, or ILC.

Patient: What exactly is invasive lobular carcinoma?

Doctor: Invasive lobular carcinoma is the second most common type of breast cancer. It starts in the lobules, which are the milk-producing glands in your breast, and it can spread to surrounding tissues. It behaves differently from the more common ductal carcinoma, so our approach to diagnosis and treatment may be a bit different.

Patient: How is it different from other breast cancers?

Doctor: ILC often grows in a more diffuse pattern, making it harder to detect on imaging and sometimes harder to feel as a lump. Because of this, we may recommend additional imaging, such as an MRI or a special PET scan, to get a clearer picture of the cancer’s size and if it has spread.

Patient: What are the next steps?

Doctor: The next step is to determine the stage of your cancer. This involves more tests—possibly blood work, an MRI, or a PET scan—to see if the cancer has spread beyond the breast. Once we have this information, we can discuss the best treatment plan for you.

Patient: What are the treatment options?

Doctor: Treatment usually starts with surgery to remove the cancer. Depending on the stage and your preferences, this could be a lumpectomy or a mastectomy. Most ILCs are hormone receptor-positive, so hormone therapy—such as tamoxifen or aromatase inhibitors—is often recommended. Some patients may also need radiation or, less commonly, chemotherapy, as ILC tends to respond less well to chemotherapy than other breast cancers.

Patient: What should I ask or consider before making a decision?

Doctor: It’s a good idea to ask about the size and location of the tumor, whether there are multiple tumors, and what additional imaging might be helpful. You should also ask about the pros and cons of each treatment, the possible side effects, and how treatment may affect your daily life. If you have concerns about the recommended treatment, seeking a second opinion is always an option.

Patient: What is the outlook for this type of cancer?

Doctor: The prognosis for ILC is generally good, especially when caught early. About 94% of women with stage I to III ILC are alive and cancer-free five years after diagnosis, and about 86% are alive and cancer-free at 10 years. The earlier we catch it, the better the outcome tends to be.

Patient: Thank you, doctor. This helps me understand what’s happening and what to expect.

Doctor: Of course. Please write down any questions you have, and bring them to our next appointment. I’m here to support you through every step.

references

[Invasive lobular carcinoma - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/invasive-lobular-carcinoma/diagnosis-treatment/drc-20373979)

[Invasive Lobular Carcinoma: Symptoms, Causes & Treatment](https://my.clevelandclinic.org/health/diseases/21180-lobular-breast-cancer#what-is-invasive-lobular-carcinoma)

[Invasive Lobular Carcinoma: Diagnosis, Treatment, & Prognosis](https://www.nationalbreastcancer.org/invasive-lobular-carcinoma/)

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## **Medullary Carcinoma Breast Cancer**

Medullary carcinoma breast cancer is a specific type of breast cancer that is characterized by the presence of medullary features when viewed under a microscope. These features include the rapid growth of tumor cells, a well-defined border between the tumor and normal breast tissue, and immune system cells within the tumor.

Although medullary carcinoma breast cancer is considered a rare subtype, it is generally associated with a better prognosis compared to other types of breast cancer. Patients with medullary carcinoma breast cancer tend to have a lower risk of recurrence and a higher survival rate.

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## **Medullary Carcinoma Breast Symptoms**

The symptoms of medullary breast carcinoma are similar to those of other types of breast cancer and may include a lump or thickening in the breast, changes in breast size or shape, nipple discharge, or skin changes on the breast. However, some patients with medullary carcinoma breast cancer may not experience any symptoms at all.

* Women need to perform regular breast self-exams and seek medical attention if they notice any unusual changes in their breasts.
* Early detection of medullary carcinoma breast cancer can lead to more successful treatment outcomes.

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## **Medullary Carcinoma Breast Treatment**

The treatment approach for medullary carcinoma breast cancer may involve a combination of surgery, chemotherapy, radiation therapy, and targeted therapy. The specific treatment plan is tailored to each patient based on factors such as the cancer stage, the tumor size, and the patient's overall health.

* Surgery is often the first line of treatment for medullary carcinoma breast cancer, to remove the tumor and surrounding tissues.
* Chemotherapy and radiation therapy may be recommended to target any remaining cancer cells and reduce the risk of recurrence.

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## **Medullary Carcinoma Breast Causes**

The exact causes of medullary breast carcinoma are not well understood, but like other types of breast cancer, certain risk factors may increase the likelihood of developing this condition. These risk factors include a family history of breast cancer, genetic mutations, hormonal factors, and lifestyle choices.

* Research is ongoing to understand the underlying causes of medullary breast carcinoma and to develop more effective prevention strategies.
* Early detection and regular screening are crucial in identifying medullary carcinoma breast cancer in its early stages.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for medullary breast carcinoma is as follows:

* Invasive carcinoma of no special type
* Chronic inflammation
* Lymphoma
* Lymphoepithelioma-like carcinoma
* Melanoma

**EPIDEMIOLOGY**

The patient’s age at presentation is younger than that for invasive ductal carcinoma NOS, with a mean age ranging from 45 to 54 years.Medullary carcinoma is unicentric in most of the patients, and bilateral carcinomas have presented in an incidence ranging from 3% to 18% of patients.Bilateral tumors are common when a family history is present.Typical medullary breast carcinoma occurs more frequently in patients with mutations of the suppressor gene BRCA-1 present

### **Surgery**

[Surgery](https://breastcancernow.org/about-breast-cancer/treatment/surgery-for-primary-breast-cancer) is usually the first treatment for medullary breast cancer.

There are 2 main types of surgery:

* Breast-conserving surgery – removal of the cancer with a margin (border) of normal breast tissue around it. It’s also known as wide local excision or lumpectomy
* Mastectomy – removal of all the breast tissue, usually including the nipple area

The type of surgery recommended depends on:

* Where the cancer is in the breast
* The size of the cancer relative to the size of the breast
* Whether more than 1 area in the breast is affected

You may need more surgery if the margin of normal tissue surrounding the cancer that was removed during the first operation is not clear. This is to make sure all the cancer has been removed. In some cases, this second operation will be a mastectomy.

Most women who have a mastectomy will have the option to have [breast reconstruction](https://breastcancernow.org/about-breast-cancer/treatment/surgery-for-primary-breast-cancer/breast-reconstruction).

#### **Surgery to the lymph nodes**

Medullary breast cancer is less likely to spread to the lymph nodes (glands) under the arm than other types of breast cancer.

Your treatment team will still want to check if any of the lymph nodes under the arm contain cancer cells. This, along with other information about your breast cancer, helps them decide whether you will benefit from any additional treatment after surgery.

To do this, your surgeon is likely to recommend an operation to remove either some of the lymph nodes (a sentinel lymph node biopsy or sample) or all of them (a lymph node clearance).

## **Doctor-Patient Conversation: Medullary Carcinoma of the Breast**

Doctor: Thank you for coming in today. I have your biopsy results, and I’d like to discuss them with you. The diagnosis is medullary carcinoma of the breast.

Patient: What does that mean? Is it a common type of breast cancer?

Doctor: Medullary carcinoma is a rare form of breast cancer, making up about 3–5% of all breast cancers. It tends to occur in younger women and is characterized by a well-defined tumor with certain unique features under the microscope, such as a prominent presence of immune cells around the tumor.

Patient: How does it behave compared to other breast cancers?

Doctor: Medullary breast cancer often grows as a distinct mass and, compared to other types, is less likely to spread to the lymph nodes under the arm. It also tends to have a better prognosis, with 10-year survival rates up to 84%—which is higher than for many other breast cancers. The cancer cells are usually larger, and the tumor often has clear boundaries when seen on scans or during surgery.

Patient: What kind of treatment will I need?

Doctor: Treatment for medullary breast cancer is similar to other invasive breast cancers and usually starts with surgery. There are two main surgical options:

* Breast-conserving surgery (lumpectomy): Removes the tumor along with a small margin of healthy tissue.
* Mastectomy: Removes all of the breast tissue, usually including the nipple area.

The choice depends on the size and location of the tumor and your personal preferences. If the tumor is large or in more than one area, a mastectomy may be recommended.

Patient: Will I need lymph node surgery?

Doctor: Even though medullary breast cancer is less likely to spread to lymph nodes, we still check them—usually with a sentinel lymph node biopsy or, in some cases, by removing several nodes. This helps us decide if you need any additional treatments after surgery.

Patient: Are there other treatments besides surgery?

Doctor: Depending on the tumor’s features—such as its size, grade, and whether it has certain hormone receptors—you may need additional treatments like chemotherapy, radiotherapy, or targeted drug therapy. Your treatment plan will be tailored to your specific situation.

Patient: What is the outlook for this type of cancer?

Doctor: The outlook for medullary breast cancer is generally very good, especially when caught early. Most people respond well to treatment and have a high chance of long-term survival.

Patient: Thank you for explaining everything.

Doctor: Of course. If you have more questions or want to discuss treatment options in detail, we can arrange another appointment. I’m here to support you through every step.

REFERENCES

[Medullary Breast Carcinoma - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK542292/#article-24902.s10)

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### **MUCINOUS CARCINOMA**

**DEFINITION AND DESCRIPTION**

Mucinous carcinoma is a rare type of cancer. In mucinous carcinoma, cancer cells form in mucin, the main component of mucus. Mucins are proteins that help with the function of healthy cells. In mucinous carcinoma, the mucin around cancer cells becomes part of the tumor.

Mucinous carcinoma can occur anywhere in your body, but it’s most common in your breast. When mucinous carcinoma occurs in your breast, it’s called colloid carcinoma. Mucinous carcinoma may also form in your lungs, colon or rectum.

### **Pure and mixed mucinous carcinoma**

Sometimes, the mucinous cancer cells are the only cancer cells present. This type is called pure mucinous carcinoma.

These mucin-surrounded cancer cells can also form along with other types of cancer cells. When this occurs, it’s called mixed mucinous carcinoma.

### **Mucinous carcinoma and adenocarcinoma?**

Adenocarcinoma starts in your mucous glands. Your mucous glands are clusters of mucous cells in the mucous membrane, which lines your digestive tract. With adenocarcinoma, people often produce too much mucin.

Mucinous carcinoma starts in the mucin, the protein that surrounds all cells. This type of cancer involves the mucin, which becomes part of the tumor.

### **How common is mucinous carcinoma?**

Mucinous carcinoma is rare. It’s most common in breast cancer, accounting for about 7% of cases. It also accounts for:

* About 3% of ovarian cancer.
* Less than 5% of lung cancer.
* About 9% of rectal cancer.
* Less than 10% of endometrial (uterine) cancer.
* About 15% of colon cancer.

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## **Symptoms and Causes**

### **What causes mucinous carcinoma?**

In general, cancer forms when your body’s cells don’t break down or grow as usual. Healthcare providers don’t know exactly what causes cancer. Some factors that can affect your risk include:

* Age: Your risk of developing certain cancers, such as breast cancer, increases as you get older.
* Environment: Exposure to secondhand smoke or certain chemicals can increase risk.
* Family history: If one of your family members had cancer, you might be more likely to develop cancer.
* Genetics: Certain gene changes (mutations) can increase your cancer risk.
* Lifestyle: Drinking alcohol, eating a low-fiber diet and having a sedentary lifestyle can be risk factors for certain cancers.

### **Symptoms of mucinous carcinoma**

Mucinous carcinoma symptoms are similar to symptoms of other cancer types. The first sign of mucinous carcinoma in your breast may be a lump in your breast tissue. You may also have:

* Armpit or breast pain.
* Breast changes, such as in size or shape.
* Nipple discharge.
* Skin swelling, puckering or dimpling.

Mucinous carcinoma can also form in your colon or rectum. The symptoms are similar to other types of colorectal cancer, including:

* Abdominal pain or cramping.
* Blood in your stool or rectal bleeding.
* Bowel habit changes, such as constipation or diarrhea.
* Unexplained weight loss.
* Weakness.

Mucinous carcinoma in your lungs may cause:

* Chest pain.
* Chronic cough.
* Coughing up blood.
* Headache.
* Hoarseness.
* Shortness of breath (dyspnea).

## **Diagnosis and Tests**

To diagnose mucinous carcinoma, your healthcare provider may use:

* Imaging tests, such as an ultrasound, MRI or CT scan.
* Mammogram, an imaging tool to evaluate breast tissue.
* Biopsy, a procedure to take a small tissue sample to examine in a lab.

## **Management and Treatment**

Mucinous carcinoma treatment depends on the cancer type and stage and your overall health. In cancer staging:

* Stage I, II or III mean you have cancer in one part of your body. The higher the stage, the more cancer has spread to surrounding tissues.
* Stage IV means cancer has spread (metastasized) to other, distant parts of your body.

Mucinous carcinoma is often less aggressive than other cancer types. Oncologists (cancer doctors) may treat it with:

* Hormone therapy to reduce your estrogen (female hormone) levels. This treatment is often effective for mucinous carcinoma of the breast.
* Surgery to remove cancer cells.
* Chemotherapy, taking medications that destroy cancer cells.
* Radiation therapy to kill or slow the growth of cancer cells.
* Targeted therapy, taking drugs that identify and attack specific parts of cancer cells.
* Immunotherapy, or medications that help your immune system detect and destroy cancer cells.

## **Outlook / Prognosis**

Many mucinous carcinomas are treatable. They’re usually less aggressive than other types of cancer. They don’t spread as quickly to your lymph nodes or other tissues.

With all types of cancer, the earlier you get treatment, the better your chances of a positive outcome. Pure mucinous carcinoma typically has a better prognosis than mixed mucinous carcinoma. In one study, the five-year survival rate of pure mucinous carcinoma was nearly 100%.

After any cancer treatment, you’ll need regular follow-ups with your healthcare provider. These visits monitor your overall health and help healthcare providers detect and treat cancer promptly if it does return (recurs).

## **Prevention**

There’s no guaranteed way to prevent mucinous carcinoma. You can reduce your risk of developing any cancer by following a healthy lifestyle:

* Achieve and maintain an optimal weight for your sex, age and body type.
* Eat a nutritious diet with fruits, vegetables, healthy fats, lean protein and whole grains.
* Exercise regularly, incorporating both strength training and aerobic exercise.
* Limit your intake of alcohol and processed meats.
* Practice safe behaviors, including safe sex and refraining from drug use or needle sharing.
* Quit smoking.

## **Common Questions**

* Do I have pure or mixed mucinous carcinoma?
* What tests do I need to diagnose mucinous carcinoma?
* What are the treatment options?
* What are the chances that mucinous carcinoma will return after treatment?

### **Is mucinous breast cancer aggressive?**

Mucinous carcinoma in the breast, especially pure mucinous carcinoma, is usually less aggressive than other types of breast cancer.

### **Can mucinous carcinoma spread?**

Yes. Mucinous carcinoma can spread to surrounding tissues or other parts of your body. But it’s less likely to spread than other types of cancer cells.

## **Epidemiology of Mucinous Carcinoma of the Breast**

* Incidence: Mucinous carcinoma is a rare subtype of invasive breast cancer, accounting for approximately 2–4% of all breast carcinomas, with reported ranges from 1% to 7% depending on the study population.
* Age Distribution: This cancer predominantly affects older women, especially those who are postmenopausal. The median age at diagnosis is typically between 62 and 70 years. It is very rarely diagnosed in women under 35 years of age, with an incidence of less than 1% in this age group.
* Gender: Mucinous carcinoma almost exclusively occurs in women.
* Prognosis: Compared to other types of invasive breast cancer, mucinous carcinoma generally has a better prognosis, with lower rates of lymph node involvement and higher long-term survival rates.
* Subtypes: There are two main subtypes—pure and mixed mucinous carcinoma. Pure mucinous carcinoma is associated with an even more favorable prognosis than the mixed type, which contains both mucinous and nonmucinous components.
* Other Features: The tumor is slow-growing and more common in perimenopausal and postmenopausal women. It is characterized by a distinct mucinous (gelatinous) appearance on pathology

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## **Differential Diagnosis of Mucinous Carcinoma of the Breast**

Key Entities to Consider:

* Mucocele-like Lesion (MLL): Benign breast lesion with mucin pools, often difficult to distinguish from mucinous carcinoma, especially on small biopsies. MLLs typically retain a myoepithelial cell layer and show benign cytomorphology, whereas mucinous carcinoma lacks myoepithelial cells in tumor nests and shows cytologic atypia.
* Mucinous Ductal Carcinoma In Situ (DCIS): Non-invasive lesion with mucin production, but without invasion into surrounding tissue.
* Solid Papillary Carcinoma: Can have mucinous features and may mimic mucinous carcinoma, but typically shows a solid growth pattern and neuroendocrine differentiation.
* Lobular Carcinoma with Extracellular Mucin: Rare, but can be confused with mucinous carcinoma due to mucin production; immunohistochemistry can help differentiate.
* Mucinous Cystadenocarcinoma: Rare primary breast tumor with abundant mucin, but with distinct histological features.
* Metastatic Mucinous Carcinomas: Tumors from other organs (e.g., gastrointestinal tract, ovary, lung) can metastasize to the breast and mimic primary mucinous carcinoma. Clinical history, immunohistochemistry, and molecular studies are crucial for distinction.
* Other Breast Malignancies with Well-Circumscribed Margins: Papillary, medullary, metaplastic carcinomas, and malignant phyllodes tumors may also appear well-circumscribed on imaging, similar to mucinous carcinoma

## **Doctor-Patient Conversation: Mucinous Carcinoma of the Breast**

Doctor: Thank you for coming in today. I have your biopsy results, and I’d like to discuss them with you. The diagnosis is mucinous carcinoma of the breast.

Patient: What does that mean? Is it a common type of breast cancer?

Doctor: Mucinous carcinoma is a rare form of breast cancer, making up about 1–4% of cases. It’s called “mucinous” because the cancer cells produce mucus, which can be seen in the tumor. This type of cancer is usually less aggressive than other forms of breast cancer and often grows more slowly.

Patient: How is it usually found?

Doctor: It’s often found as a lump during a breast exam or on a mammogram. We confirm the diagnosis with a biopsy, where we look for the characteristic pools of mucin under the microscope.

Patient: What are the treatment options?

Doctor: Treatment usually starts with surgery. Depending on the size and location of the tumor, we may recommend:

* Breast-conserving surgery (lumpectomy), where only the tumor and a small margin of healthy tissue are removed, or
* Mastectomy, where all of the breast tissue is removed.  
  We’ll also check the lymph nodes under your arm to see if the cancer has spread, but mucinous carcinoma is less likely to spread to lymph nodes than other types.

Patient: Will I need other treatments?

Doctor: That depends on certain features of your tumor. Most mucinous carcinomas are hormone receptor-positive, meaning they grow in response to hormones like estrogen or progesterone. If that’s the case, hormone therapy—such as tamoxifen or aromatase inhibitors—can help reduce the risk of the cancer coming back. Radiation therapy is often recommended after breast-conserving surgery. Chemotherapy is less commonly needed, especially for pure mucinous carcinoma, unless the tumor has more aggressive features or has spread to lymph nodes.

Patient: What is the outlook?

Doctor: The prognosis for mucinous carcinoma is generally very good, especially if it’s the “pure” type and hasn’t spread to the lymph nodes. Five-year survival rates for pure mucinous carcinoma are close to 100%.

Patient: What happens after treatment?

Doctor: After treatment, you’ll have regular follow-up appointments to monitor your recovery and check for any signs that the cancer might return. Most people with mucinous carcinoma do very well after treatment.

Patient: Thank you, doctor. That helps me understand what’s happening.

Doctor: You’re welcome. If you have more questions or want to talk through your treatment options in more detail, I’m here to help.

references

[Mucinous Carcinoma: Definition, Pathology & Treatment](https://my.clevelandclinic.org/health/diseases/22975-mucinous-carcinoma#overview)

<https://breastcancernow.org/about-breast-cancer/diagnosis/types-of-breast-cancer/mucinous-breast-cancer>

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### **papillary thyroid cancer (PTC)**

Papillary thyroid cancer begins in the follicular cells in your thyroid that produce thyroglobulin (a protein). It’s the most common type of thyroid cancer.

Your thyroid is a small, butterfly-shaped gland located at the front of your neck under your skin. It’s a part of your endocrine system and controls many of your body’s important functions by producing and releasing (secreting) certain hormones.

PTC tends to grow very slowly and usually develops in only one lobe of your thyroid gland.

There are several subtypes of papillary thyroid cancers. Of these, the follicular subtype (also called mixed papillary-follicular variant) is the most common. Other subtypes of papillary cancer aren’t as common and tend to grow and spread more quickly. They include:

* Columnar.
* Tall cell.
* Insular.
* Diffuse sclerosis.

Papillary thyroid cancer is also called papillary thyroid carcinoma.

### **Who does papillary thyroid cancer affect?**

Papillary thyroid cancer can affect anyone, but it most commonly occurs in middle-aged adults. Women are more likely to develop PTC than men.

Although PTC is rare in children, it’s still the most common pediatric thyroid cancer.

### **How common is papillary thyroid cancer?**

Thyroid cancer is fairly common, and papillary thyroid cancer is the most common type. It accounts for 80% to 85% of all thyroid cancer cases.

### **Is papillary thyroid cancer serious?**

While all cancer types are serious in that they require medical treatment and have the potential to spread to other parts of your body (metastasize), papillary thyroid cancer has the best overall prognosis of all thyroid cancer types.

PTC can often be treated successfully and is rarely fatal.

### **Where does papillary thyroid cancer spread first?**

Papillary thyroid cancer is most likely to spread (metastasize) to the lymph nodes in your neck first. Lymph nodes are small bean-shaped structures that are part of your body’s lymphatic system and immune system.

### **How often does papillary thyroid cancer spread?**

Even though papillary thyroid cancer grows slowly, PTC often spreads to the lymph nodes in your neck.

About 30% of people have metastatic papillary thyroid cancer (that has spread to other parts of their body) at diagnosis.

## **Symptoms and Causes**

The main sign of papillary thyroid cancer is a painless lump or nodule on your thyroid gland. PTC usually doesn’t cause any other symptoms.

In rare cases, you may experience pain in your neck, jaw or ear from PTC. If the nodule is large enough to compress your windpipe or esophagus, it may cause difficulty with breathing or swallowing.

### **What causes papillary thyroid cancer?**

Scientists still don’t know the exact cause of papillary thyroid cancer, but they have identified risk factors that increase your risk of developing PTC, including radiation exposure and certain genetic conditions.

#### **Radiation exposure and papillary thyroid cancer**

The rates of papillary thyroid cancer are higher in people who have a history of exposure to significant ionizing radiation. This exposure could be due to:

* High-dose external radiation treatments to your neck, especially during childhood, used to treat cancer or some noncancerous conditions.
* Radiation exposure from nuclear plant disasters. The Chernobyl nuclear accident in 1986 led to a 3- to 75-fold increase in PTC cases in fallout regions.

#### **Genetics and papillary thyroid cancer**

A few genetic (inherited) conditions are associated with PTC, including:

* Familial adenomatous polyposis (Gardner syndrome): Familial adenomatous polyposis (FAP) is a rare hereditary condition in which a person develops several precancerous polyps in their large intestine (colon and rectum). People with FAP are also at an increased risk of developing tumors in other areas of their body, including their thyroid. Gardner syndrome and FAP are due to an inherited mutation in the *APC* gene.
* Werner syndrome: Werner syndrome is a rare condition that’s characterized by the appearance of unusually accelerated aging (progeria). People with Werner syndrome have an increased predisposition to cancers. The most common cancers in Werner syndrome are thyroid cancers. More than 80 different mutations of the *WRN* gene have been identified in people with this condition.
* Carney complex type 1: Carney complex is a condition characterized by an increased risk of several types of tumors, including thyroid tumors. Mutations in the *PRKAR1A* gene cause most cases of Carney complex.

Only 5% of all papillary thyroid cases are associated with these genetic conditions.

## **Diagnosis and Tests**

Papillary thyroid cancer usually presents as a lump or nodule on your thyroid gland. You may notice it, or your healthcare provider may discover it during a routine neck examination. Sometimes, the nodule is discovered incidentally (accidentally) by imaging tests you get for other medical reasons.

Your healthcare provider will likely order the following tests to help diagnose PTC:

* Imaging tests: Your provider may order imaging tests to identify the nodule on your thyroid. These tests might include thyroid ultrasound, CT (computed tomography) scan and/or magnetic resonance imaging (MRI).
* Fine needle aspiration (needle biopsy): Your provider will likely want to take a small tissue sample, called a biopsy, from the nodule on your thyroid using a very thin needle. A pathologist will look at the tissue under a microscope to see if there are cancer cells and, if so, what type of thyroid cancer it is.

Your healthcare provider may also recommend genetic counseling to see if you have a genetic condition that may have caused PTC and may cause other types of tumors.

## **Management and Treatment**

Treatments for papillary thyroid cancer depend on the tumor size and whether the cancer has spread (metastasized).

Surgery is the most common treatment for PTC. Depending on the tumor’s size and location, your surgeon may remove part of your thyroid gland (lobectomy) or all of your gland (thyroidectomy). If you have cancer present in the lymph nodes of your neck, your surgeon may remove the affected lymph nodes at the time of the initial thyroid surgery or as a second procedure.

If you have a total thyroidectomy, you’ll need to take thyroid hormone replacement medication for the rest of your life.

Additional treatments for PTC include:

* Radioiodine (radioactive iodine) therapy: Thyroid cells and papillary thyroid cancer cells absorb iodine, a mineral found in some food. Because of this, healthcare providers sometimes use a radioactive form of iodine to destroy all remaining normal thyroid tissue and potentially destroy residual cancerous thyroid tissue after a thyroidectomy.
* Radiation therapy: Radiation kills cancer cells and stops them from growing. External radiation therapy uses a machine to deliver strong beams of energy directly to the tumor site. Internal radiation therapy (brachytherapy) involves placing radioactive seeds in or around the tumor.
* Chemotherapy: Intravenous (IV) or oral chemotherapy drugs kill cancer cells and stop cancer growth. Very few people diagnosed with thyroid cancer will ever need chemotherapy.

### **Side effects and complications of papillary thyroid cancer treatment**

Permanent hypothyroidism (low thyroid hormone levels) is an expected side effect of thyroidectomy and radioiodine therapy. Because of this, you’ll need to take replacement thyroid hormone medication for the rest of your life if you undergo either or both of these treatments.

Possible complications of thyroid surgery include:

* Infection.
* Accidental removal of or damage to your parathyroid glands, which help regulate your blood calcium levels.
* Damage to your recurrent laryngeal nerve, which runs behind your thyroid gland, resulting in hoarseness and a weak voice.

Potential side effects of radioactive iodine therapy include:

* Nausea and vomiting.
* Sialadenitis (swollen salivary gland).
* Transient thyrotoxicosis (excess thyroid hormone in your body).
* Pulmonary fibrosis (a lung disease that happens when lung tissue becomes damaged and scarred).
* Infertility.
* Small risk of leukemia, breast or bladder cancer.

## **Outlook / Prognosis**

Overall, the prognosis of papillary thyroid cancer is excellent, especially if you’re younger than 40 at diagnosis and have a small tumor. PTC can often be treated successfully and is rarely fatal, even if it has spread to lymph nodes in your neck.

Factors that may lead to a worse prognosis include:

* Being older than 55 years at diagnosis.
* Having a large tumor.
* If the cancer has spread to distant parts of your body.
* If you have a rare subtype of PTC, which are typically more aggressive, including the tall cell variant, diffuse sclerosis variant or solid variant.

### **Can you survive papillary thyroid cancer?**

The survival rate for papillary thyroid cancer is excellent. More than 90% of adults with PTC survive at least 10 to 20 years after treatment.

## **Prevention**

Most people with thyroid cancer have no known risk factors, so it’s not possible to prevent most cases of papillary thyroid cancer.

Radiation exposure, especially in childhood, is a known PTC risk factor. Because of this, healthcare providers no longer use radiation to treat less serious diseases. Imaging tests, such as X-rays and CT scans, also expose children to radiation, but at much lower doses. It’s not clear how much they might increase the risk of PTC.

If you have a family history of thyroid cancer, you may want to get genetic counseling to see if you have any inherited conditions that put you at a higher risk of developing PTC. If this is the case, your healthcare provider may recommend getting preventive (prophylactic) surgery to remove your thyroid gland before cancer develops.

## **When should I see my healthcare provider about papillary thyroid cancer?**

If you’ve been diagnosed with papillary thyroid cancer, you’ll need to see your healthcare team regularly to monitor your treatment progress. You’ll also need long-term monitoring every six to 12 months to look for cancer recurrence (when it comes back) for at least five years.

If you had your thyroid removed and/or had radioactive iodine therapy as part of treatment, you’ll need to take thyroid hormone medication for the rest of your life. Your healthcare provider will want to monitor your thyroid hormone levels throughout your life to make sure your medication dosage is working for you.

### **Papillary Thyroid Cancer Staging**

Papillary thyroid cancers are not all alike. Some are big and some are small. Some have spread to lymph nodes and some have not. To separate out the cancers that are easy to cure from those that are more difficult to cure, doctors have come up with a grading or "staging" system. All cancers have their own staging system, but papillary thyroid cancer has a staging system that is not like other cancers. This staging system for papillary thyroid cancer takes into account the age of the patient. The staging system also includes the size of the papillary thyroid cancer in the thyroid gland itself and whether or not the cancer has spread into lymph nodes around the thyroid or sides of the neck. The staging system for papillary thyroid cancer also includes whether or not the cancer has spread into the fat and muscles around the thyroid (called local extension). Finally, this staging system includes the “differentiation” of the cancer which is what it looks like under a microscope and whether or not the thyroid cancer cells look mature or young and more “angry”. The last component of papillary thyroid cancer staging is the presence of distant metastases, which means whether the cancer has spread to distant (far way) areas like the lungs. The stage of the cancer will determine how aggressive the operation needs to be, and other things like whether or not radioactive iodine should be given.

Several staging systems have been proposed for PTC and continue to evolve. The most commonly used are:

For patients less than 45 years:

* Stage l: any Tm, any N, M0 (cancer localized to the thyroid)
* Stage ll: Any T, any N, M1 (cancer spread to cervical nodes or distant organs)

For patients older than 45 years:

* Stage l: T1, N0, M0 (cancer less than 2 cm)
* Stage ll: T2, N0, M0, and T3 (cancer localized to the thyroid that is between 2 to 4 cm)
* Stage lll: T4, N0, M0, and any T, N1, M0 (lesion more than 4 cm and spread limited to the neck)
* Stage lV: Any T, any N, M1 (cancer spread outside the neck and to distant organs)

**NCCN Guidelines for Total Thyroidectomy**

* Known distant metastases
* History of radiation
* Extrathyroidal extension
* Bilateral nodules
* The tumor measures more than 4 cm
* Poorly differentiate lesion
* Positive cervical lymph nodes

Routine cervical node dissection continues to be debated. Some literature notes fewer recurrences, but other studies have noted a higher incidence of recurrent nerve injury.

## **Alternative Names**

Papillary carcinoma of the thyroid; Papillary thyroid cancer; Papillary thyroid carcinoma

**DIFFERENTIAL DIAGNOSIS**

The primary differential diagnoses of PTC are:

* Reactive changes following fine-needle aspiration.This condition characteristically shows nuclear enlargement, chromatin clearing, and micro-nucleoli similar to the nuclei of PTC.
* Severe chronic lymphocytic thyroiditis, where the reactive atypia is attributed to inflammation, results in nuclear morphology similar to that of PTC.
* Adenomatoid nodules
* Diffuse hyperplasia
* Dyshormonogenetic goiter
* Follicular adenoma
* Follicular thyroid carcinoma
* Medullary thyroid carcinoma
* Metastatic tumors

EPIDEMIOLOGY

PTC is the predominant form of thyroid cancer, accounting for 80 to 85% of all thyroid cancer cases. In a report based on the Surveillance, Epidemiology, and End Results (SEER) database from 1975 to 2012, the incidence of PTC increased from 4.8 to 14.9 per 100,000. A recent report of autopsy results showed no difference in the prevalence of subclinical thyroid cancer through lifespan and different age groups. One of the latest thoughts in the medical community is that there is an obvious overdiagnosis of thyroid cancer in general that might even result in overtreatment without necessarily changing the ultimate prognosis and mortality from the disease. The overdiagnosis is usually due to frequent incidental finding of micro cancers of the thyroid gland in routine imaging studies, and the overtreatment is due to the slow-changing mentality of the medical force that is still using aggressive surgical therapy as definite treatment of thyroid cancer versus the newest more conservative approach of observation or more limited surgical intervention. PTC occurs predominantly in middle-aged adults with a 3 to 1 female-to-male ratio; the median age at presentation is 50 years. Even though rare in children, PTC is still the most common pediatric thyroid malignancy. It affects Whites more commonly than Blacks

## **Genomic Data of Papillary Thyroid Carcinomas (PTC)**

Key Genetic Alterations:

* BRAF Mutations:  
  The most common mutation in PTC is the BRAF V600E mutation, found in approximately 45–60% of cases. This mutation activates the MAPK signaling pathway, promoting tumor growth and progression. BRAF mutations are strongly associated with the classical and tall cell variants of PTC and are linked to more aggressive clinical features, including extrathyroidal extension, lymph node metastasis, and higher risk of recurrence.
* RET/PTC Rearrangements:  
  RET chromosomal rearrangements (fusion genes) are another hallmark of PTC, particularly in children and adolescents and in cases with prior radiation exposure. RET/PTC1 is most common in classical PTC, while RET/PTC3 is more often found in the solid variant. RET fusions account for about 10% of PTC cases.
* RAS Mutations:  
  RAS gene mutations (NRAS, HRAS, KRAS) are more frequently observed in the follicular variant of PTC and are the second most common genetic alteration in differentiated thyroid cancers. They also activate the MAPK pathway and are associated with less aggressive tumor behavior compared to BRAF mutations.
* TERT Promoter Mutations:  
  Mutations in the TERT promoter are less common but are associated with aggressive disease and a higher risk of recurrence. Patients with TERT or BRAF mutations have a 3-fold increased risk of cancer recurrence compared to those without these mutations.
* Other Genetic Events:
  + PAX8/PPARγ rearrangements are more common in follicular variants.
  + TP53 and PI3K pathway mutations are rare in PTC but can be seen in more aggressive or poorly differentiated tumors.
  + Novel gene fusions, such as KCTD5-RET, have also been identified.
  + Ultra-deep sequencing reveals additional low-frequency mutations in genes like RBM10

## **Doctor-Patient Conversation: Papillary Thyroid Carcinoma**

Doctor: Thank you for coming in today. I have your biopsy results, and I’d like to talk through them with you. The diagnosis is papillary thyroid carcinoma, which is the most common type of thyroid cancer.

Patient: What does that mean? Is it serious?

Doctor: Papillary thyroid carcinoma is a type of cancer that starts in the thyroid gland, located in your neck. The good news is that it’s usually slow-growing and highly treatable, especially when caught early. Most people with this diagnosis do very well after treatment.

Patient: How did this happen? I only noticed a lump in my neck.

Doctor: That’s very common. Many people notice a lump or swelling in the neck, or sometimes have trouble swallowing. We usually confirm the diagnosis with an ultrasound and a fine needle biopsy, which is what you had.

Patient: What are the treatment options?

Doctor: The main treatment is surgery to remove the thyroid gland, called a thyroidectomy. Sometimes, if the cancer has spread to nearby lymph nodes, we remove those as well. After surgery, many patients receive radioactive iodine treatment to destroy any remaining thyroid tissue or cancer cells. You’ll also need to take thyroid hormone replacement pills for life, since your body won’t make thyroid hormone after surgery.

Patient: What is the outlook?

Doctor: The outlook for papillary thyroid carcinoma is excellent. Most people are cured with surgery and, if needed, radioactive iodine. Regular follow-up is important, but long-term survival rates are very high.

Patient: Will I have to make big changes to my life?

Doctor: You’ll need to take thyroid hormone pills every day, and we’ll monitor your levels regularly. Most people return to their normal activities after recovering from surgery. Some people experience fatigue or other symptoms as we adjust your medication, but these are manageable.

Patient: Thank you for explaining everything.

Doctor: Of course. If you have more questions or want to talk through your treatment plan in more detail, I’m here to support you every step of the way.

REFERENCES

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[Papillary Thyroid Carcinoma - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK536943/#article-30159.s10)

[Papillary Thyroid Cancer (PTC): Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/23382-papillary-thyroid-cancer-ptc#overview)

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## **Papillary carcinoma breast**

**Definition**

The term papillary breast cancer can refer to a number of different types of breast cancer. These include:

* Invasive papillary breast cancer
* Invasive micropapillary breast cancer
* Intracystic/encapsulated/encysted papillary cancer
* Papillary ductal carcinoma in situ

They’re often found alongside other types of breast cancer.

The treatment and [outlook (prognosis)](https://breastcancernow.org/about-breast-cancer/diagnosis/primary-breast-cancer-prognosis) for papillary breast cancer will depend on the type of papillary breast cancer as well as its features.

Papillary breast cancer is not the same as the benign (not cancer) condition [intraductal papilloma](https://breastcancernow.org/about-breast-cancer/breast-lumps-and-benign-not-cancer-breast-conditions/intraductal-papilloma).

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## **Symptoms of papillary breast cancer**

As with most types of breast cancer, the symptoms of papillary breast cancer can include:

* A lump or swelling in the breast
* Changes to the nipple
* A change in the size of the breast

[Breast screening](https://breastcancernow.org/about-breast-cancer/screening-tests-and-scans/breast-screening) can pick up cancer before there are any symptoms. You may have been diagnosed with papillary breast cancer after attending breast screening without having any symptoms.

## 

## **Diagnosis**

Papillary breast cancer is diagnosed using [a range of tests](https://breastcancernow.org/about-breast-cancer/screening-tests-and-scans). These may include:

* A mammogram
* An ultrasound scan
* A core biopsy of the breast and sometimes lymph nodes
* A fine needle aspiration (FNA) of the breast and sometimes lymph nodes

## **Treatment for papillary breast cancer**

Treatment will depend on the type of papillary breast cancer you have and if another type of breast cancer is also found.

The treatments you’re offered will also depend on the features of the cancer such as the:

* Size
* Grade
* Hormone receptor status
* HER2 status

### **Surgery**

If you have papillary breast cancer, surgery is likely to be the first treatment you’re offered.

There are 2 main types of surgery:

* Breast-conserving surgery, also known as wide local excision or lumpectomy – removal of the cancer with a margin (border) of normal breast tissue around it
* Mastectomy – removal of all the breast tissue usually including the nipple area

The type of surgery you’re recommended will depend on:

* Where the cancer is in the breast
* The size of the cancer relative to the size of your breast
* Whether more than 1 area in the breast is affected

If you have breast-conserving surgery, it’s important the cancer is removed with a border (margin) of healthy breast tissue around it. This is to reduce the risk of any cancer cells being left behind. If there are cancer cells at the margin, you may need further surgery to remove more tissue, which may be a mastectomy.

Most women who have a mastectomy will have the option to have breast reconstruction.

#### **Surgery to the lymph nodes under the arm**

If you have an invasive type of papillary breast cancer, your treatment team will want to check if any of the lymph nodes (glands) under the arm contain cancer cells.

This, along with other information about your breast cancer, helps them decide whether you’ll benefit from any additional treatment after surgery.

Find out more about [surgery to the lymph nodes](https://breastcancernow.org/about-breast-cancer/treatment/surgery-for-primary-breast-cancer).

If you have intracystic/encapsulated/encysted papillary breast cancer or papillary carcinoma in situ, you’re less likely to have surgery to the lymph nodes. This is because these types rarely spread to the lymph nodes.

### **Other treatments**

Depending on the type of papillary breast cancer you have, you may need other treatments after surgery. These can include:

* Radiotherapy
* Hormone therapy
* Chemotherapy
* Targeted therapy
* Bisphosphonates

These treatments aim to reduce the risk of breast cancer returning in the same breast or spreading somewhere else in the body. Which treatments you’re recommended will depend on your individual situation.

Treatments given after surgery are called adjuvant treatments.

Some of these treatments may be given before surgery. This is known as neoadjuvant or primary treatment.

#### **Radiotherapy**

If you have breast-conserving surgery, you’ll usually be offered [radiotherapy](https://breastcancernow.org/about-breast-cancer/treatment/radiotherapy-for-primary-breast-cancer) to the breast. This is to reduce the risk of cancer coming back in the same breast.

Radiotherapy is sometimes given to the chest wall after a mastectomy.

#### **Hormone (endocrine) therapy**

Some breast cancers use the hormone oestrogen in the body to help them grow. These are known as oestrogen receptor positive or ER-positive breast cancers.

Hormone therapies block or stop the effect of oestrogen on breast cancer cells. Different hormone therapy drugs do this in different ways.

Hormone therapy will only be prescribed if your breast cancer is ER-positive.

#### **Chemotherapy**

Chemotherapy destroys cancer cells by affecting their ability to divide and grow.

Chemotherapy may be recommended for some people who have an invasive type of papillary breast cancer.

#### **Targeted therapies**

This is a group of drugs that block the growth and spread of cancer. They target and interfere with processes in the cells that help cancer grow.

The type of [targeted therapy](https://breastcancernow.org/about-breast-cancer/treatment/targeted-biological-therapy) you’re given will depend on the features of your breast cancer.

The most widely used targeted therapies are for [HER2](https://breastcancernow.org/about-breast-cancer/diagnosis/her2) positive breast cancer. HER2 is a protein that helps cancer cells grow.

Papillary cancers are much less likely to be HER2 positive than some other types of breast cancer.

#### **Bisphosphonates**

Bisphosphonates are a group of drugs that can reduce the risk of breast cancer spreading in women who have been through the menopause. They can be used if the menopause happened naturally or because of breast cancer treatment.

Your treatment team can tell you if bisphosphonates would be suitable for you.

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## **After treatment**

You'll continue to be monitored after your hospital-based treatments (such as surgery, chemotherapy or radiotherapy) finish. This is known as [follow-up](https://breastcancernow.org/about-breast-cancer/treatment/follow-up-after-treatment).

Whether you had breast-conserving surgery or a mastectomy (with or without reconstruction), it's important to be aware of any changes to the breast, chest or surrounding area.

The area around your scar may feel lumpy, numb or sensitive. This means you'll need to get to know how it looks and feels so you know what’s normal for you. This will help you feel more confident about noticing changes and reporting them early to your breast care nurse, treatment team or GP.

Having breast cancer in one breast means the risk of developing cancer in the other breast ([a new primary breast cancer](https://breastcancernow.org/about-breast-cancer/diagnosis/second-primary-diagnosis)) is slightly higher than in someone who's never had breast cancer. It’s important to be aware of any new changes in the other breast and to report these as soon as possible.

## 

## **Epidemiology of Papillary Carcinoma of the Breast**

* Incidence:  
  Papillary carcinoma of the breast is a rare subtype, accounting for approximately 0.5–2% of all breast cancers. Invasive papillary carcinoma (IPC) specifically represents less than 1–2% of invasive breast cancer cases.
* Age and Gender:  
  This cancer typically presents in postmenopausal women, with a mean age at diagnosis between 61 and 69 years. While rare, it can also occur in men; male cases constitute about 3–14% of reported papillary carcinomas, which is a higher proportion than seen in other breast cancer types.
* Clinical Presentation:  
  Most patients present with a palpable mass or nipple discharge. About 22–34% of patients have nipple discharge at diagnosis.
* Histological Subtypes:  
  Papillary carcinoma encompasses several forms, including:
  + Invasive papillary carcinoma (IPC)
  + Encapsulated (intracystic) papillary carcinoma (EPC)
  + Solid papillary carcinoma (SPC)
  + Papillary ductal carcinoma in situ (DCIS)
* Tumor Characteristics:  
  These tumors are usually well-circumscribed, often located in the retro-areolar/subareolar region (about 50% of cases), and tend to be lower grade with smaller tumor size and less frequent lymph node involvement compared to other breast cancers.
* Prognosis:  
  Papillary carcinoma of the breast generally has an excellent prognosis. Five-year overall survival rates are high, with studies reporting 97–98% for invasive and non-invasive forms. Disease-specific survival is also superior to that seen in invasive ductal carcinoma.
* Risk Factors:  
  Predisposing factors include older age, family history, genetic predisposition, dietary factors, alcohol consumption, weight gain, and hormonal/endocrine influences

**Common Mutations and Pathways:**

PIK3CA and AKT1 Mutations:  
There is a high prevalence of mutations in the PI3K-AKT-mTOR pathway, particularly in encapsulated papillary carcinoma (EPC) and other papillary neoplasms. Roughly two-thirds of benign papillary neoplasms are impacted by PIK3CA and AKT mutations.

ZFPM1 Mutations:  
Recurrent somatic mutations in the ZFPM1 gene are characteristic of EPC and often occur alongside PI3K-AKT-mTOR pathway mutations.

TP53 and 16q23 Loss:  
Loss of heterozygosity (LOH) at 16q23 and TP53 deletion are associated with malignant transformation in papillary lesions.

Copy Number Alterations:  
Papillary carcinomas often show loss of chromosome 16q and gain of 16p and 1q, similar to low-grade, ER-positive invasive ductal carcinoma of no special type (IDC-NST). However, papillary carcinomas generally have fewer genetic aberrations and lower p53 expression than IDC-NST.

DNA Ploidy:  
DNA-aneuploidy, along with changes at specific chromosomal loci (such as chromosomes 3, 7, 17, and X), is more common in malignant papillary carcinomas than in benign papillomas.

Other Genetic Findings:

BRCA1/2, p53, PTEN:  
A minority (5–10%) of breast malignancies, including papillary types, arise due to germline mutations in BRCA1, BRCA2, p53, and PTEN.

IDH2 and TET2 Mutations:  
Specific rare subtypes, such as solid papillary carcinoma with reverse polarity, may harbor IDH2 and TET2 mutations

## **Differential Diagnosis of Papillary Carcinoma of the Breast**

## Main Entities in the Differential Diagnosis

* Benign Intraductal Papilloma
  + Features: Well-circumscribed, presence of myoepithelial cells along fibrovascular cores.
  + Distinction: Malignant papillary neoplasms lack an intact myoepithelial cell layer within the papillae.
* Atypical Papilloma
  + Features: Papilloma with areas of atypical proliferation not sufficient for DCIS.
  + Distinction: May require extensive histologic sampling and immunohistochemistry for definitive diagnosis.
* Papillary Ductal Carcinoma In Situ (DCIS)
  + Features: Non-invasive, may arise within a papilloma; surrounded by myoepithelial cells.
  + Distinction: Invasive papillary carcinoma shows stromal invasion, higher nuclear grade, and necrosis.
* Encapsulated (Intracystic) Papillary Carcinoma
  + Features: Well-circumscribed, surrounded by a fibrous capsule; may have low or intermediate nuclear grade.
  + Distinction: Invasion is indicated by tumor cells infiltrating beyond the capsule.
* Solid Papillary Carcinoma
  + Features: Expansile nodules with solid pattern, delicate fibrovascular cores, and possible neuroendocrine features.
  + Distinction: May be noninvasive or invasive; neuroendocrine markers can assist in diagnosis.
* Invasive Micropapillary Carcinoma
  + Features: Aggressive, morula-like epithelial clusters surrounded by empty spaces (reverse polarity).
  + Distinction: Lacks fibrovascular cores, more than 90% of tumor consists of these clusters.
* Other Breast Carcinomas
  + Includes colloid (mucinous) carcinoma, medullary carcinoma, and invasive ductal carcinoma, which may mimic papillary carcinoma on imaging or limited biopsy.
* Metastatic Papillary Carcinomas
  + Tumors from ovary, lung, or thyroid with papillary features can metastasize to the breast.
  + Distinction: Immunohistochemistry for markers such as PAX8, WT1, TTF1, and thyroglobulin can help identify non-mammary origin

## **Doctor-Patient Conversation: Papillary Carcinoma of the Breast**

Doctor: Thank you for coming in today. I have your pathology results, and I’d like to discuss them with you. The diagnosis is papillary carcinoma of the breast, which is a rare type of breast cancer.

Patient: What does that mean? Is it serious?

Doctor: Papillary carcinoma makes up less than 2% of all breast cancers and tends to occur more often in postmenopausal women. It’s characterized by finger-like projections of tumor cells. The good news is that this type generally has a very favorable prognosis, especially when detected early.

Patient: How is it usually found?

Doctor: Most people notice a lump in the breast or sometimes nipple discharge—about a third of patients have bloody nipple discharge. The tumor is often located just below the nipple, and imaging or a biopsy helps confirm the diagnosis.

Patient: What are the treatment options?

Doctor: Treatment usually starts with surgery. The two main options are:

* Lumpectomy: Removing just the tumor and a small margin of healthy tissue, preserving most of the breast.
* Mastectomy: Removing the entire breast, which may be recommended if the tumor is large or if you prefer this option.

We may also check the lymph nodes under your arm to see if the cancer has spread. Sometimes, additional treatments like radiation or hormone therapy are recommended, depending on the tumor’s features and your overall health.

Patient: Will I need chemotherapy?

Doctor: Chemotherapy is less commonly needed for papillary carcinoma compared to other types of breast cancer, especially if the tumor is small, hormone receptor-positive, and hasn’t spread to lymph nodes. Your treatment plan will be personalized based on your specific case.

Patient: What is the outlook?

Doctor: The prognosis for papillary carcinoma of the breast is excellent. Most people do very well after treatment, and the five-year survival rate is around 90% or higher for invasive papillary carcinoma. Regular follow-up is important to monitor for any signs of recurrence.

Patient: Thank you for explaining everything.

Doctor: You’re welcome. If you have more questions or want to talk through your treatment options in more detail, I’m here to support you every step of the way.

references

[Papillary breast cancer | Breast Cancer Now](https://breastcancernow.org/about-breast-cancer/diagnosis/types-of-breast-cancer/papillary-breast-cancer)

### 

### **Hepatocellular carcinoma (HCC)**

Hepatocellular carcinoma is the most common form of liver cancer. It’s an aggressive (fast-growing) cancer most common in people with advanced liver disease, like cirrhosis of the liver. Increasingly, people diagnosed with HCC have a liver condition that sometimes leads to cirrhosis called metabolic dysfunction-associated steatotic liver disease (MASLD).

In the beginning, hepatocellular carcinoma grows slowly. Surgery to remove the tumor or a liver transplant can treat HCC in its early stages. But most people don’t learn they have it until it’s advanced and spreading more quickly. Eventually, it can lead to liver failure. At this point, HCC is challenging for providers to treat.

Given how serious it is, you should receive regular checks for signs of HCC if you have cirrhosis or MASLD.

#### **How common is HCC?**

HCC accounts for about 85% to 90% of all primary liver cancers. “Primary” means the cancer starts in your liver (as opposed to spreading to your liver, as with metastatic cancer). It’s the sixth most common type of cancer diagnosis and the third leading cause of cancer-related deaths.

HCC is two to three times more common in men. Most people diagnosed are 60 or older.

## **Symptoms and Causes**

Tumors may not cause symptoms in the early stages. But as HCC progresses, you may notice:

* Fullness or a knot under your ribs on your right side (symptoms of an enlarged liver).
* Fullness under your ribs on your left side (symptoms of an enlarged spleen).
* Eyes and skin turning yellow (signs of jaundice).
* A stomach that feels swollen, like it’s filling up with fluid.
* Loss of appetite or feeling full after a small meal.
* Unexplained weight loss.
* Nausea and vomiting.
* Itching.

Many conditions cause similar symptoms, and most aren’t as serious as hepatocellular cancer. So, try not to panic if you experience one or more of them. But if symptoms last longer than two weeks, it’s best to see a healthcare provider.

### **What causes hepatocellular carcinoma?**

Most people diagnosed with HCC have cirrhosis of the liver (approximately 80%) although some have a condition that can lead to cirrhosis of the liver. In some instances, the condition never progresses to cirrhosis, but people still develop HCC.

With these conditions, unmanaged long-term liver inflammation can lead to severe scarring and, eventually, HCC.

#### **Risk factors for HCC**.

Factors that may increase the risk of hepatocellular carcinoma include:

* **Older age.** Hepatocellular carcinoma is more common in older adults.
* **Infection with hepatitis B virus or hepatitis C virus.** Ongoing or previous infection with the hepatitis B virus or hepatitis C virus increases the risk of hepatocellular carcinoma.
* **Cirrhosis.** Cirrhosis is a progressive and irreversible condition that causes scar tissue to form in the liver. It increases the chances of developing hepatocellular carcinoma.
* **Certain inherited liver diseases.** Some liver diseases that can run in families may increase the risk of hepatocellular carcinoma. Examples include hemochromatosis and Wilson's disease.
* **Excess fat in the liver.** Nonalcoholic fatty liver disease, also called metabolic dysfunction-associated steatotic liver disease, happens when fat builds up in the liver. People with this condition are at an increased risk of hepatocellular carcinoma.
* **Diabetes.** People with this blood sugar condition have a greater risk of hepatocellular carcinoma than those who don't have diabetes.
* **Obesity.** People with obesity have a higher risk of cirrhosis and excess fat in the liver. These conditions increase the risk of hepatocellular carcinoma.
* **Exposure to aflatoxins.** Aflatoxins are poisons produced by molds that grow on crops that are stored poorly. Crops, such as grains and nuts, can become contaminated with aflatoxins, which can end up in foods made of these products.
* **Excessive alcohol consumption.** Consuming more than a moderate amount of alcohol daily over many years can lead to irreversible liver damage and increase the risk of hepatocellular carcinoma.
* **Smoking cigarettes.** People who smoke cigarettes are at an increased risk of hepatocellular carcinoma.

## **Diagnosis and Tests**

Your healthcare provider will do a physical exam. They’ll also ask about your medical history, symptoms and lifestyle.

Tests to help confirm a diagnosis include:

* Blood tests: Your provider may check your blood for signs of HCC, like high alpha-fetoprotein (AFP) levels. Elevated AFP may signal HCC or a condition that can lead to HCC, like a hepatitis infection or cirrhosis of the liver.
* Imaging scans: Imaging procedures, like an ultrasound, computed tomography (CT) scan, magnetic resonance imaging (MRI) or angiography can show tumors (or signs of a tumor) inside your liver.
* Liver biopsy: Your provider may biopsy a liver tumor to test the tissue for cancer cells. You may need this test if your bloodwork results and imaging scans aren’t definitive enough for a diagnosis.

A biopsy is a procedure to remove a sample of tissue for testing in a lab. For hepatocellular carcinoma, the biopsy uses a needle to get the tissue sample. During a liver biopsy, a healthcare professional puts a needle through the skin and into the cancer. The health professional uses the needle to draw out a sample of cells from the liver.

The sample is tested in a lab to see if it is cancer. Other special tests give more details about the cancer cells. Your healthcare team uses this information to make a treatment plan.

Not everyone needs a biopsy to diagnose hepatocellular carcinoma. Sometimes healthcare teams make the diagnosis using the results of other tests.

HCC is an unusual cancer because in people with cirrhosis, providers can make the diagnosis based on the tumor(s) having certain features on an MRI or CT scan without needing to do a biopsy.

#### **How is HCC staged?**

Cancer staging for HCC allows your healthcare provider to determine how advanced it is. It also helps them plan treatments and determine your prognosis (outlook). To stage HCC, providers consider:

* How big the tumor is.
* How much it’s grown into nearby tissue (including your lymph nodes).
* Whether it’s spread beyond your liver (metastatic cancer).
* How advanced the underlying liver disease is.

## **Management and Treatment**

Treatments include:

* Surgery: The surgical treatments for HCC are hepatectomy (removing the diseased part of your liver) or a liver transplant. You may receive a hepatectomy if the tumor is only limited to one part of your liver. If your liver isn’t healthy enough for a hepatectomy, a liver transplant may be an option

Other procedures on the liver can help treat hepatocellular carcinoma. These treatments may be used in people who can't have surgery to remove the cancer. These other liver procedures for hepatocellular carcinoma include:

* **Radiofrequency ablation.** Radiofrequency ablation uses electric current and heat to hurt the cancer cells. During this procedure, a healthcare professional places small needles into the cancer. The needles deliver hot temperatures that hurt the cancer cells.
* **Cryoablation.** Cryoablation uses cold to hurt the cancer cells. During the procedure, a healthcare professional places small needles into the cancer. The needles deliver cold temperatures that hurt the cancer cells.
* **Chemoembolization.** Chemoembolization gives chemotherapy medicines directly to the cancer. It also uses medicine that blocks the flow of blood to the cancer. Blocking the blood flow to the cancer may cause the cancer to shrink, grow more slowly or not grow at all.
* **Radioembolization.** Radioembolization uses tiny beads that hold radiation. The healthcare team puts the beads into a blood vessel that goes to the liver. The beads give off radiation directly to the cancer.
* **Radiation therapy.** Radiation therapy treats cancer with powerful energy beams. The energy can come from X-rays, protons or other sources. The beams can target the cancer in the liver.

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* Ablation therapy: Providers performing ablation use a special needle to burn tumors. The needle may direct energy that’s extremely hot (microwaves or radiofrequency waves) or freezing cold.
* Embolization: Embolization implants a substance directly into the arteries supplying the tumor, stopping blood flow. Chemoembolization implants a substance that contains chemotherapy drugs. Radioembolization implants small beads of radiation.
* Radiation therapy: Providers may recommend radiation therapy to treat small tumors that they can’t remove with surgery or destroy using ablation. Stereotactic body radiation therapy (SBRT) is a specific type of radiation treatment that providers use to treat HCC.
* Immunotherapy: Immunotherapy medicines also treat advanced HCC. They help your immune system identify and fight cancer cells.
* Targeted therapy: Targeted therapy medicines treat advanced HCC. This treatment switches off the signal that tells cancer cells to keep growing.

Targeted therapy for cancer is a treatment that uses medicines that attack specific chemicals in the cancer cells. By blocking these chemicals, targeted treatments can cause cancer cells to die.

Targeted therapy may be used after surgery to kill any remaining cancer cells. For those with advanced hepatocellular carcinoma that can't be removed with surgery, targeted therapy may be an option.

Your healthcare provider may suggest participating in a clinical trial to try new HCC treatments. They may also recommend palliative care to help you manage cancer symptoms and treatment side effects. Palliative care can improve your experience whether you’re living with long-term disease or receiving treatment for early-stage, curable HCC.

## **Outlook / Prognosis**

Surgery to remove the tumor or a liver transplant are the best options for a cure. If surgery isn’t an option, there are other treatments to ease your symptoms, slow the tumor’s growth and help you live longer.

Researchers continue to search for new ways to cure hepatocellular carcinoma that can’t be removed with surgery. In the meantime, new treatments, like immunotherapy and targeted therapy, continue to improve the life expectancy of people diagnosed with advanced HCC.

### **Survival rate for hepatocellular carcinoma**

The five-year relative survival rate (people alive five years after their diagnosis) for people with HCC is 21%.

But many factors contribute to life expectancy, including how advanced HCC is, your liver’s overall health and your response to treatment. Some studies show that receiving care in a hospital that commonly treats HCC can improve survival rates.

Every case of HCC is different. Your healthcare provider is your best resource for offering insight into what you might expect based on your condition.

## **Prevention**

There are several ways you can reduce your risk of developing HCC. You can:

* Get your hepatitis B vaccination, or get regular check-ups if you already have hepatitis B.
* See your healthcare provider if you think you may have been exposed to hepatitis C. (It’s curable with treatment.)
* Work with your provider to manage metabolic conditions associated with MASLD. Maintaining a weight that’s healthy for you by eating healthy foods is key.
* Cut back on the amount of alcohol you drink.
* Stop smoking if you do.

## **Living With**

HCC can feel like an overwhelming diagnosis. It’s completely normal to feel uncertain about what happens next. But there are steps you can take to cope with your diagnosis and advocate for yourself.

You can:

* Keep track of questions and concerns. Asking questions about your condition and treatment helps you understand what to expect and what you can do to help yourself.
* Focus on managing stress. Cancer is stressful. Activities such as meditation, relaxation exercises or deep breathing may help ease your stress. Getting plenty of rest during this time is also essential for managing stress.
* Adjust what you eat. Your treatments might affect your appetite. Try to eat healthy meals and snacks. Talk to a nutritionist or a dietitian if you’re having trouble eating certain foods or need guidance on what foods to eat or avoid.
* Reach out for emotional support. Cancer can be lonely. Sometimes, it’s hard talking to loved ones who don’t know firsthand what it’s like living with a cancer diagnosis. Your healthcare provider can direct you to support groups where you can share your feelings with people living with cancer who better understand.

### **When should I see my healthcare provider?**

Contact your provider if you have symptoms of HCC for two or more weeks or if existing symptoms get worse. Don’t skip check-ups if you belong to a high-risk group and your healthcare provider recommends screenings for HCC.

Catching HCC early, when surgery can treat it, delivers the best possible outcomes.

## **Diagnostic Considerations**

Other problems to consider in the differential diagnosis include the following:

* Dysplastic nodules in cirrhosis
* Fibrous nodular hyperplasia
* Metastatic disease
* Primary hepatic lymphoma

## 

## **Differential Diagnoses**

* Cholangiocarcinoma
* Cirrhosis
* Hepatocellular Adenoma (Hepatic Adenoma)

## 

## **Epidemiology**

In the United States, liver cancer is the most rapidly increasing cancer in both men and women, with incidence rates more than tripling since 1980; from 2006 to 2015, the rate increased by about 3% per year. For 2024, the American Cancer Society (ACS) estimates that 41,630 new cases of liver cancer (including intrahepatic bile duct cancers) will be diagnosed; approximately three-fourths of those will be HCC.

Liver and intrahepatic bile duct cancers are the 13th most common type of cancer,but are the fifth most common cause of cancer deaths in men in the US, and the seventh most common in women.The ACS estimates that 29,840 deaths will occur from liver cancer in 2024. According to Surveillance, Epidemiology, and End Results (SEER) program data, liver and intrahepatic bile duct cancers account for 2.1% of all new cancer cases but 4.8% of all cancer deaths.

In the US, the median age at diagnosis is 66 years. Most cases occur in men: Incidence rates per 100,000 persons are 14.1 in men and 5.2 in women. Incidence rates increase with age; 31.6% of cases are in persons age 55-64 years and 33.7% in those 65-74 years.Globally, the incidence of liver cancer among men and women who are younger than 30 years and those aged 30 to 59 years has declined, largely due to national hepatitis B virus (HBV) vaccination programs.

By racial and ethnic group, rates are highest in American Indian/Alaska Natives, followed by Hispanics, Asians/Pacific Islanders, then Blacks, and whites.

Worldwide, liver cancer was the sixth most common cancer and the third most common cause of cancer deaths in 2020, with an estimated 905,677 new cases and 830,180 deaths. The incidence was highest in East Asia, at 17.9 per 100,000 population (26.9 in males and 8.9 in females), followed by Micronesia, northern Africa, Southeast Asia, and Melanesia. The incidence was lowest in south-central Asia (3.0 per 100,000) and South America (4.4 per 100,000). By comparison, the incidence rate was 6.9 per 100,00 in northern America and 5.6 per 100,000 in western Europe. Overall, the incidence rate of liver cancer is approximately three times higher in males than in females. Mortality figures mirror the incidence figures. [1]

In the United Kingdom, both the incidence and mortality rates of hepatocellular carcinoma (HCC) have risen dramatically. From 1997 to 2017, incidence rates of HCC increased 5.9% per year, rising from 3.03 to 9.22 per 100,000 in men, and from 0.87 to 2.17 per 100,000 in women. Mortality rates per 100,000 population rose from 2.11 to 6.74 in men, and from 0.69 to 1.61 in women.

Steady declines in HCC mortality are predicted for East Asia. In contrast, Northern and Central Europe, North America, and Latin America are showing unfavorable trends. According to an analysis of data from the Global Burden of Disease (GBD) Study, the number of liver cancer cases increased nearly threefold in older men and more than twofold in older women (aged 60 years or more) from 1990 to 2017. The increase consisted mainly of cases secondary to nonalcoholic steatohepatitis (NASH; popularly known as fatty liver disease).

## **Staging**

A number of staging systems have been used for HCC. These systems may incorporate clinical, pathologic, radiologic, or treatment response factors. Each of the systems has its strengths and weaknesses; none is universally accepted.

The prognosis in patients with HCC reflects both tumor characteristics (ie, size, location, tumor biology) and the degree of underlying liver disease. The traditional pathologic TNM (tumor-node-metastasis) staging system, while helpful in determining a prognosis in patients undergoing resection, is not as useful in planning treatment, because it fails to include measures of the severity of the liver disease. However, the tumor size is predictive of outcome, as it predicts the likelihood of major venous involvement.

Likewise, the Child-Pugh-Turcotte score predicts perioperative survival after resection, but it does not incorporate tumor size, number, and location, which have important implications for respectability and treatment. Among the scales that integrate the tumor and liver disease characteristics, the Barcelona Clinic Liver Cancer (BCLC) system, [37] the Japan Integrated Staging System, and the Cancer of the Liver Italian Program (CLIP) are the most widely used staging systems.

### BCLC algorithm

The BCLC system is very useful in deciding among potential treatment options and correlates best with patient outcome among the major staging systems.

In the BCLC system, stage 0 patients have lesions smaller than 2 cm, normal bilirubin levels, and normal portal pressure measurements. These patients can often undergo resection safely with excellent long-term survival.

Patients with larger tumors (ie, single tumors < 5 cm or multiple [≤ 3] tumors < 3 cm) are considered for resection if they have preserved liver function or for transplantation if they have decompensated cirrhosis.

In patients whose tumor exceeds these measurements, palliative therapy can be offered depending upon hepatic reserve. Fewer than 10% of these patients survive longer than 3 years.

### CLIP scoring system

A score of 0-2 is assigned for each of the 4 features listed below; a cumulative score ranging from 0-6 is the CLIP score.

*Child-Pugh class:*

* Class A = 0
* Class B = 1
* Class C = 2

*Tumor morphology:*

* Uninodular and extension less than 50% = 0
* Multinodular and extension less than 50% = 1
* Massive and extension greater than 50% = 2

*Alpha-fetoprotein:*

* Less than 400 = 0
* Greater than 400 = 1

*Portal vein thrombosis:*

* Absent = 0
* Present = 1

*Estimated survival based on CLIP score*

Patients with a total CLIP score of 0 have an estimated survival of 31 months; those with score of 1, about 27 months; score of 2, 13 months; score of 3, 8 months; and scores 4-6, approximately 2 months.

Similarly, the NCCN guidelines recommend screening with US, with or without AFP testing, every 6 months in patients with cirrhosis due to any of the following

* Hepatitis B or C
* Alcohol
* Genetic hemochromatosis
* NAFLD
* Stage 4 primary biliary cholangitis
* Alpha-1-antitrypsin deficiency
* Other causes

surveillance in hepatitis B virus (HBV) carriers without cirrhosis. The following patients are at additional risk:

* Carriers with family history of HCC
* Asian men ≥40 y
* Asian women ≥50 y
* African/North American Blacks

:

Cost-effectiveness studies suggest that surveillance of HCC is warranted in all cirrhotic patients, irrespective of its etiology, as long as their liver function and comorbidities allow curative or palliative treatments.

Surveillance of hepatitis-infected patients without cirrhosis is also advocated, especially in HBV carriers with serum viral load > 10 000 copies/mL or HCV-infected patients with bridging fibrosis.

For nodules identified on US that are < 1 cm, repeat US at intervals of 3-6 months; if no growth is observed over a period of up to 2 years, revert to routine surveillance.

A lesion of ≥10 mm on ultrasound or an AFP level > 20 ng/mL should trigger recall procedures for the diagnosis of HCC.

For multiphase CT and MRI, key imaging features include the following:

* Size ≥1 cm
* Arterial phase hyperenhancement
* Depending on exact size, a combination of washout, threshold growth, and capsule appearance

If these criteria are not present but HCC or other malignancy is considered probable, then a liver biopsy should be considered for diagnosis. In patients without cirrhosis, the diagnosis of HCC cannot be made by imaging, even if the scan shows hypervascularity in the arterial phase with washout in the portal venous or delayed phase; biopsy is required in these cases.

When a lesion is suspicious for malignancy, but multiphasic CT or MRI results do not meet imaging criteria for HCC

In patients who are not considered to be at high risk for HCC (ie, patients who do not have cirrhosis, chronic HBV, or a previous history of HCC)

In patients with conditions associated with formation of nonmalignant nodules that may be confused with HCC on imaging (eg, cardiac cirrhosis; congenital hepatic fibrosis; cirrhosis due to a vascular disorder such as Budd-Chiari syndrome, hereditary hemorrhagic telangiectasia, or nodular regenerative hyperplasia)

* In patients with elevated CA 19-9 or carcinoembryonic antigen (CEA), in order to rule out intrahepatic cholangiocarcinoma

**biopsy:**

* If the diagnosis of HCC cannot be established from routine histology, staining for several biomarkers, including the diagnostic panel of glypican-3 (GPC3), heat shock protein 70 (HSP70), and glutamine synthetase, can be used to help distinguish HCC from high-grade dysplastic nodules.
* If the biopsy is negative, the lesion should be followed by imaging at 3- to 6-month intervals until the nodule disappears, enlarges, or develops features characteristics of HCC.
* If the lesion enlarges but remains atypical for HCC, the biopsy should be repeated.

**diagnosis and management of focal liver lesions (FLLs)**

Patients with cirrhosis in whom an ultrasound shows a lesion of > 1 cm should undergo an MRI or triple-phase CT scan.

* Patients with chronic liver disease who are at a very high risk for HCC and who present with a solid FLL must be considered to have HCC until proved otherwise.
* HCC can be diagnosed with CT or MRI if the typical characteristics are present.
* If an FLL in a patient with cirrhosis does not have typical characteristics of HCC, then a biopsy should be performed.
* The diagnosis of HCC is based on histological analysis and/or contrast-enhanced imaging findings.
* The diagnosis can be established if the typical vascular hallmarks of HCC (hypervascularity in the arterial phase with washout in the portal venous or delayed phase) are identified in a nodule of > 1 cm diameter using one of those two modalities in a cirrhotic patient.
* Based on techniques such as diffusion-weighted imaging and the use of hepatobiliary contrast agents, MRI may allow identification and stratification of nodules as high-risk nodules (either HCC not displaying the typical imaging hallmarks features or high-grade dysplastic nodules).
* For contrast-enhanced ultrasound (CEUS), an overlap between the vascular profile of HCC and cholangiocarcinoma has been described. However, recent data suggest CEUS as a suitable technique to diagnose HCC noninvasively in the setting of liver cirrhosis.
* When tumor biopsy fails to demonstrate a correlate for a focal lesion, a second tumor biopsy, a different contrast-enhanced imaging modality or (if amenable) direct resection of the lesion may be considered, according to tumor size.
* Histopathological diagnosis of tumor biopsies relies on standard (hematoxylin and eosin [H&E]) and special stains (eg, reticulin), and—if required—immunohistochemistry (IHC).
* It is important to distinguish combined HCC/cholangiocarcinoma from HCC, because treatments for the two differ; however, the mixed differentiation features might not be visible in the biopsy. In addition, although HCC is commonly negative for cytokeratin 19 (CK19), significant expression of CK19 may be present in HCC and is considered as a sign of poor prognosis in HCC.
* In highly differentiated HCC, definitive signs of malignancy (interstitial or vascular invasion) are frequently absent from biopsy. Further consented histological criteria (trabecular alterations—more than two cell broad trabeculae, pseudoglands, reticulin loss, capsule formation) and cytological criteria (increased nuclear/cytoplasmic ratio; ie, ‘nuclear crowding’, increased cytoplasmic basophilia) support the diagnosis of HCC.
* IHC should be carried out in unclear cases: capillarization of sinusoids could be assessed using CD34 IHC.
* Further immunohistochemical markers have been shown to improve the diagnosis of highly differentiated HCC, including glutamine synthetase, GPC3, circulating tumor cells (CTC) , EZH2, and HSP70.

### Staging

The tumor-node-metastasis (TNM) classification of the American Joint Cancer Committee/Union for International Cancer Control/ (AJCC/UICC) is useful only in patients who undergo surgical resection, which is a small minority of patients.

Only the NCCN guidelines follow TNM for staging.

Since most patients have unresectable disease and prognosis depends more on the state of the liver than on the size of the tumor,

prognostic prediction and treatment stratification.

The BCLC staging system attempts to overcome the limitations of previous staging systems by identifying prognostic stages (0 and A through D) based on five variables:

* Tumor stage
* Functional status of the liver
* Physical status
* Cancer-related symptoms

See Table 4, below.

Table 4. Barcelona Clinic Liver Cancer staging

| Stage | Criteria |
| --- | --- |
| 0 – Very Early | Child-Pugh class A  Single < 2 cm nodule  ECOG PS 0-1 |
| A – Early | Child-Pugh class A-B  Single or 2-3 nodules < 3 cm  ECOG PS 0-1 |
| B – Intermediate | Child-Pugh class A-B  Multinodular  ECOG PS 0-1 |
| C - Advanced | Child-Pugh class A-B  Portal vein invasion, N1, M1  ECOG PS 0-2 |
| D - Terminal | Child-Pugh class C  Any T, N, or M  ECOG PS > 2 |
| ECOG PS = Eastern Cooperative Oncology Group Performance Status | |

The BCLC staging system also links each HCC stage to appropriate treatment modalities, as follows:

* Patients with early-stage HCC (stage 0 and A) may benefit from curative therapies (ie, liver transplantation, surgical resection, radiofrequency ablation).
* Patients with intermediate-stage(stage B) or advanced-stage (stage C) disease may benefit from palliative treatments (ie, transcatheter arterial chemoembolization and sorafenib)
* Patients with end-stage disease (stage D) are offered supportive care and palliation

### Treatment

AASLD guidelines divide therapeutic options into curative and noncurative interventions.Curative therapies, which offer the chance of long-term response and improved survival, include the following:

* Surgical resection
* Orthotopic liver transplantation
* Ablative techniques (eg, thermal ablation)

Non Curative therapies, which attempt to prolong survival by slowing tumor progression, include the following:

* Transarterial chemoembolization (TACE)
* Transarterial radioembolization (TARE)
* Stereotactic body radiation therapy (SBRT)
* Systemic chemotherapy

The guidelines agree that resection is the treatment of choice for solitary tumors in non-cirrhotic patients or cirrhotic patients with well-preserved liver function. Pre- or post-resection adjuvant therapy is not recommended.

The guidelines further concur that liver transplantation is the best available curative option for patients with early-stage non-resectable HCC who meet the Milan criteria (single tumors ≤5 cm in diameter or no more than three nodules ≤3 cm in diameter in patients with multiple tumors). Ablation should be considered as definitive treatment for patients with stage 0-A tumors who are not candidates for resection or transplantation. NCCN and AASLD guidelines also recommend ablation as a possible bridge therapy for patients awaiting transplantation.

The AASLD recommends TACE as first-line non curative therapy for BCLC stage B HCC. For stage BCLC disease, sorafenib or lenvatinib is recommended as first-line therapy.

For patients with unresectable HCC who are not candidates for transplantation, NCCN recommendations for first-line systemic therapy are as follows

* Sorafenib is the preferred therapy for Child-Pugh Class A (category 1) or B7 HCC
* Lenvatinib is a preferred therapy for Child-Pugh Class A only
* Systemic chemotherapy (category 2B)

Recommended agents for subsequent-line therapy if disease progression occurs are as follows

* Regorafenib (Child-Pugh Class A only) (category 1)
* Cabozantinib (Child-Pugh Class A only) (category 1)
* Ramucirumab (alpha fetoprotein ≥400 ng/mL only) (category 1)
* Nivolumab (Child-Pugh Class A or B7)
* Sorafenib (Child-Pugh Class A or B7) (after first-line lenvatinib)
* Pembrolizumab (Child-Pugh Class A only) (category 2B)
* Larotrectinib and entrectinib (for *NTRK* gene fusion–positive HCC)

ASCO recommendations for first-line systemic therapy of advanced HCC are as follows:

* Atezolizumab/bevacizumab may be offered to most patients with Child-Pugh class A, Eastern Cooperative Oncology Group performance score (ECOG PS) 0-1, and following management of esophageal varices, when present, according to institutional guidelines.
* Patients who have contraindications to atezolizumab and/or bevacizumab may be offerered tyrosine kinase inhibitor (TKI) therapy with sorafenib or lenvatinib

Recommendations for second-line therapy are as follows:

* TKI therapy (ie, sorafenib, lenvatinib, cabozantinib, or regorafenib) may be recommended for patients who received first-line therapy with atezolizumab/bevacizumab.
* In patients who received first-line therapy with sorafenib or lenvatinib, second-line therapy with another TKI (cabozantinib or regorafenib), ramucirumab (if alpha fetoprotein level is ≥ 400 ng/mL), or atezolizumab/bevacizumab may be recommended for appropriate candidates.
* Pembrolizumab or nivolumab may reasonably be considered in appropriate patients who received first-line therapy with sorafenib or lenvatinib; those agents may be especially beneficial for patients who have contraindications to or cannot tolerate TKIs.

:

* For first-line treatment, in patients with preserved liver function who are not eligible for locoregional therapy or resection or who have metastatic disease, consider atezolizumab plus bevacizumab over sorafenib; if they are not candidates for atezolizumab/bevacizumab, consider either lenvatinib or sorafenib.
* For second-line treatment, in patients with preserved liver function who are not eligible for locoregional therapy or resection or who have metastatic disease and who had progression of disease on sorafenib, consider cabozantinib, pembrolizumab, or regorafenib.
* For second-line treatment, in patients with preserved liver function and alpha fetoprotein (AFP) > 400 ng/mL who are not eligible for locoregional therapy or resection or who have metastatic disease, who had progression of disease on sorafenib, consider using ramucirumab.
* In patients with poor liver function who are not eligible for locoregional therapy or resection or who have metastatic disease, the AGA suggests against routine use of sorafenib.
* In patients undergoing curative surgical resection or curative local ablation for HCC, the AGA suggests against adjuvant therapy with sorafenib.
* In patients undergoing TACE, the AGA suggests against adjuvant therapy with sorafenib or bevacizumab.

Guidelines from the International Stereotactic Radiosurgery Society advise that patients with liver-confined HCC and tumors < 3 cm can be considered for SBRT, with favorable local control and survival outcomes, while in those with HCC ≥3 cm, SBRT can be performed with the expectation of durable long-term local control. SBRT can be performed when the pretreatment liver function is Child-Pugh class A or B7; in patients with Child-Pugh class B8 or higher—and particularly class C—SBRT should be delivered with caution. SBRT with 1-9 fractions is recommended.

Updated 2021 ESMO guidelines provide stage-based recommendations for standard-of-care treatments for HCC.For stage 0-A (single tumor any size, or up to three nodules ≤3 cm, preserved liver function, ECOG PS 0), recommendations are as follows:

* Resection (if remnant liver will have adequate size and function)
* Transplantation (if tumor size ≤5 cm, number of nodules ≤3)
* Thermal ablation (if tumor ≤ 3 cm and not adjacent to vessels or bile duct)
* TACE (if contraindications to resection and ablation are present; may be used as bridge to transplantation

For stage B (multinodular, preserved liver function, ECOG PS 0), ESMO recommends TACE, if tumor size is 5-10 cm and tumor nodules are accessible to supra-selective catheterization.

For stage C (portal invasion, extrahepatic spread, preserved liver function, ECOG PS 0-2), ESMO recommends atezolizumab plus bevacizumab, or sorafenib or lenvatinib, as first-options. Standard after sorafenib:

* Cabozantinib
* Regorafenib (not recommended for patients without previous exposure to a tyrosine kinase inhibitor [TKI naive])
* Ramucirumab (recommended only in patients with an AFP level ≥400 ng/mL)

Options after atezolizumab plus bevacizumab or lenvatinib:

* Sorafenib
* Lenvatinib
* Cabozantinib
* Regorafenib (not recommended for TKI-naive patients)
* Ramucirumab (recommended only in patients with an AFP level ≥400 ng/mL)

For stage D (end-stage liver disease, ECOG PS 3-4), ESMO guidelines recommend best supportive care

### **What questions should I ask my healthcare provider?**

You’ll likely have several questions throughout your diagnosis and treatment.

How well is my liver working?  
Your liver function is assessed using blood tests that measure levels of albumin and bilirubin, as well as other markers. Two main scoring systems are used:

* Child-Pugh score: Considers albumin, bilirubin, INR (clotting), and the presence of ascites or encephalopathy.
* ALBI (Albumin-Bilirubin) grade: Uses only albumin and bilirubin for a more objective assessment.  
  These scores help your care team understand how well your liver is working and guide treatment decisions.

What stage is my cancer?  
Staging considers the size and number of tumors, whether cancer has spread to blood vessels, lymph nodes, or other organs, and your liver function. Imaging (CT, MRI) and blood tests help determine the stage. Staging is important for choosing the best treatment and predicting outcomes.

Can my cancer be cured?  
Cure is possible for some patients, especially if the tumor is small, has not spread, and your liver is working well. Curative treatments include surgical removal of the tumor, liver transplantation, or ablation (destroying the tumor with heat or chemicals). If the cancer is more advanced or the liver is severely damaged, treatments may focus on controlling the disease and symptoms rather than cure.

What are my treatment choices?  
Treatment options depend on the stage of your cancer and your liver function. They may include:

* Surgery: Removing part of the liver (resection) or liver transplantation.
* Ablation: Destroying tumors with heat, cold, or chemicals.
* Embolization: Blocking blood supply to the tumor.
* Targeted therapy and immunotherapy: Medicines that attack cancer cells or boost your immune system.
* Radiation therapy: Less commonly used, but an option in some cases.  
  Your care team will recommend the best approach based on your specific situation.

What are the side effects of each treatment?

* Surgery: Risks include bleeding, infection, and reduced liver function.
* Ablation/Embolization: May cause pain, fever, or temporary liver dysfunction.
* Targeted therapy/immunotherapy: Can cause fatigue, high blood pressure, skin changes, diarrhea, or immune-related side effects.
* Radiation: May cause fatigue, nausea, or damage to nearby tissues.  
  Your doctor will discuss the risks and benefits of each treatment with you.

How will treatment affect my daily life?  
The impact depends on the treatment:

* Surgery or transplantation: Requires hospital stay and recovery time.
* Ablation/embolization: Usually outpatient or short hospital stay, with some recovery at home.
* Medications (targeted/immunotherapy): Often taken at home, but regular monitoring is needed.
* Side effects: Some treatments may cause fatigue or other symptoms that affect your daily activities, but many people can continue much of their normal routine.

How will we know if treatment is working?  
Your care team will monitor you with:

* Imaging tests (CT, MRI): To see if the tumor is shrinking or stable.
* Blood tests: Including alpha-fetoprotein (AFP) levels, which may go down if treatment is working.
* Regular check-ups: To assess symptoms and liver function

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### **Cholangiocarcinoma (bile duct cancer)**

Cholangiocarcinoma is a rare cancer that starts in your bile ducts. Bile ducts are thin tubes that bring bile (a fluid that helps you digest fats) from your liver and gallbladder to your small intestine.

Cholangiocarcinoma is an aggressive cancer, which means it spreads fast. Most people receive a cholangiocarcinoma diagnosis after it’s already spread outside of their bile ducts. At this point, bile duct cancer is difficult to treat, and the prognosis (chance of recovery) is usually poor.

Experts are continually researching and developing new treatments that can slow cancer spread and improve the outlook associated with cholangiocarcinoma.

#### **What are the types of bile duct cancer?**

There are three types of cholangiocarcinoma:

* Intrahepatic cholangiocarcinoma is bile duct cancer inside your liver.
* Perihilar (hilar) cholangiocarcinoma is bile duct cancer in your hilum. The hilum is the area just outside your liver where the smaller bile ducts from inside your liver merge to form a larger duct called the common hepatic duct. It’s the most common form of cholangiocarcinoma. Another name for perihilar cholangiocarcinoma is a Klatskin tumor.
* Distal cholangiocarcinoma is bile duct cancer that starts outside your liver, in the ducts closer to your small intestine.

Perihilar cholangiocarcinoma and distal cholangiocarcinoma are also known as extrahepatic bile duct cancers because they form outside your liver (“extra”-hepatic) instead of inside your liver (“intra”-hepatic).

#### **How common is this condition?**

Cholangiocarcinoma is rare. About 8,000 people in the United States develop this cancer each year. It’s most common in people around age 70.

Worldwide, cholangiocarcinoma is more common in Southeast Asia. Bile duct cancer is a complication of clonorchiasis, a chronic (long-term) infection associated with a Chinese liver fluke parasite.

## **Symptoms and Causes**

Cholangiocarcinoma symptoms don’t usually start until the cancer advances and blocks a bile duct. Symptoms of bile duct cancer include:

* Abdominal pain.
* Fever.
* Fatigue.
* Itchy skin.
* Jaundice (skin and whites of eyes turn yellow).
* Dark urine.
* Light-colored or greasy stools.
* Nausea and vomiting.
* Unexplained weight loss.

Cholangiocarcinoma isn’t usually painful in the early stages. But a large tumor can cause pain that may feel concentrated in the right side of your abdomen, underneath your ribs. For some people, the pain may shift to other regions in their abdomen or back.

But this type of pain is common in many conditions, not just bile duct cancer. It’s important to see a healthcare provider to determine what’s causing unusual abdominal pain.

### **What causes cholangiocarcinoma?**

Experts don’t know exactly what causes cholangiocarcinoma. But health conditions that cause chronic (long-term) inflammation in your bile ducts may play a role.

Ongoing damage from inflammation can cause changes in cell DNA. DNA contains the instructions that tell cells how to behave. Damaged DNA can cause problems with how cells grow and divide, creating tumors that damage tissue. These changes probably aren’t inherited (passed down from biological parents to their children). Instead, they likely happen during a person’s lifetime.

#### **Risk factors of cholangiocarcinoma**

You may be more likely to develop cholangiocarcinoma if you have:

* Structural abnormalities where your bile duct and pancreatic duct meet.
* Bile duct stones or choledochal cyst disease (bile duct cysts).
* Clonorchiasis (infection with a Chinese liver fluke parasite).
* Chronic ulcerative colitis.
* Cirrhosis of the liver.
* Hepatitis B or hepatitis C.
* Human immunodeficiency virus (HIV).
* Inflammatory bowel disease (IBD).
* Metabolic dysfunction-associated steatotic liver disease.
* Primary sclerosing cholangitis (inflammation and scarring that blocks your bile ducts).

Additional risk factors include:

* Alcohol use disorder.
* Diabetes.
* Obesity.
* Smoking.

Exposure to toxins (especially chemicals used in rubber plants or automotive factories).

## **Diagnosis and Tests**

A healthcare provider will evaluate your symptoms, review your medical history and do a physical exam.

Tests for cholangiocarcinoma may include:

* Liver function tests: These liver tests check your blood for high levels of substances, such as elevated liver enzymes, that might indicate your liver isn’t working as it should. High levels may also mean you have a bile duct blockage.
* Tumor marker tests: These tests check your blood or urine for tumor markers — substances that might mean you have cancer. High levels of carbohydrate antigen (CA) 19-9 or carcinoembryonic antigen (CEA) may be signs of bile duct cancer.
* Imaging tests: An abdominal ultrasound is usually the first imaging test you’ll need if your provider suspects bile duct cancer. You may also need a CT scan or an MRI, including a specialized MRI called magnetic resonance cholangiopancreatography (MRCP).
* Endoscopic tests: These tests use an endoscope (a thin, flexible tube with a camera) to examine your bile ducts. While you’re sedated (in a light sleep), the endoscope goes into your mouth and down to your small intestine so your provider can see your bile ducts up close. Tests include endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP).
* Percutaneous transhepatic cholangiography (PTC): A PTC is a procedure that can be used to view bile duct blockages related to cholangiocarcinoma and drain the blockage. During the procedure, your provider will deliver a contrast dye directly into your bile ducts and liver. The dye causes blockages to show up more clearly on an X-ray. They’ll place a tube into the bile duct so it can drain. A PTC is usually only for people who can’t have an ERCP.

If test results indicate cancer, your healthcare provider will perform a biopsy to confirm the diagnosis. A biopsy removes a tissue sample so it can be tested for cancer. Your provider can take samples during an ERCP or PTC by inserting a small needle through your skin.

If you do have cholangiocarcinoma, your provider may perform tests on your tissue biopsy and blood (liquid biopsy) to check for genetic changes in cancer cells (biomarkers). Cholangiocarcinoma tumors can have important biomarkers. If they’re present, you may be eligible for special cancer treatments that target these cells for destruction (targeted therapy).

#### **How is cholangiocarcinoma staged?**

Cancer staging is an important part of a bile duct cancer diagnosis. It allows your healthcare provider to determine how much cancer is in your body. Staging helps your provider plan treatment and determine your prognosis.

Staging guidelines are different for each type of cholangiocarcinoma. But in general, bile duct cancer staging looks at the size of the tumor and whether cancer has spread from the bile ducts to your:

* Blood vessels.
* Lymph vessels and lymph nodes.
* Organs near your bile ducts, like your liver or gallbladder.
* Distant organs, such as your lungs, bones or abdominal cavity.

The staging scale ranges from stage 0 to stage 4. The least advanced and most treatable is Stage 0, or carcinoma in situ. This means you have abnormal cells that could become cholangiocarcinoma, but haven’t yet. Stage 4 is the final (or most advanced) stage of cholangiocarcinoma. At this stage, the cancer is metastatic. It’s spread beyond your bile ducts to distant parts of your body.

## **Management and Treatment**

Cholangiocarcinoma treatment depends on where it’s located and if it has spread. Surgery can treat bile duct cancers that haven’t spread. But most bile duct cancers have spread by the time they’re diagnosed.

If surgery alone won’t eliminate cholangiocarcinoma, your healthcare provider may recommend a combination of treatments to slow cancer growth or provide palliative care that relieves symptoms.

Cholangiocarcinoma treatment may include:

* Surgery: Removes all or part of your bile duct or affected organs. Surgery can also help treat a blocked duct that’s causing symptoms. Your provider may place a stent (small, hollow tube) to drain it or reroute the flow of bile past the blockage.
* Liver transplant: Replaces your liver with a donor liver. A transplant is one potential cure for early-stage perihilar cholangiocarcinoma.
* Radiation therapy: Uses radiation to kill cancer cells or shrink tumors. You may need external beam radiation therapy (EBRT), which uses a machine outside your body to direct radiation toward the tumor. Or your provider may implant tiny beads of radiation (called Y90) in the blood vessels supplying the tumor to shrink it. This is called transarterial radioembolization (TARE).
* Chemotherapy (chemo): Uses drugs to kill cancer cells or shrink tumors. Systemic chemotherapy sends the medicine through your entire body. Transarterial chemoembolization (TACE) implants tiny beads of chemo into the blood vessels near your tumor to shrink it. Hepatic artery chemo-infusion (HAI) uses a pump to inject chemo into the artery that supplies blood to your liver.
* Targeted therapy: Zeroes in on specific proteins on cancer cells. Some people with bile duct cancer have abnormal proteins that cause cells to grow out of control. Targeted therapies block the abnormal proteins that fuel cancer growth.
* Immunotherapy: Helps your body’s immune system fight cancer. In bile duct cancer, some cancer cells contain a protein that prevents immune cells from attacking. Immunotherapy disables this protein so immune cells can attack the cancer.
* Clinical trials: Studies that test the effectiveness of new cancer treatments or new combinations of existing treatments. If your cancer is too far advanced for surgical removal, your provider may recommend taking part in a clinical trial.

## **Outlook / Prognosis**

The outlook (prognosis) for people with cholangiocarcinoma is usually poor.

The five-year survival rate for cholangiocarcinoma that hasn’t spread outside of the bile ducts ranges from 18% to 23%. That number drops to 2% to 3% for cancer that’s spread beyond bile ducts.

Still, it’s important to remember that new cancer treatments are continually improving survival rates and the experiences of people living with cancer. Five-year survival rates reporting on statistics from previous years don’t reflect these developments.

Talk to your healthcare provider about your prognosis based on your cancer diagnosis, including the type of cholangiocarcinoma and its stage.

#### **How curable is bile duct cancer?**

Bile duct cancer is curable in the early stages if your provider can surgically remove all affected tissue. At this point, a liver transplant may also be a potential option for curing cholangiocarcinoma.

But only a small amount of bile duct cancers are curable because they’re usually not diagnosed until the cancer has already spread. At this point, it’s impossible to get rid of cholangiocarcinoma with surgery alone.

## **Prevention**

There’s no way to prevent bile duct cancer, but you can reduce your risk by protecting your liver (and bile ducts) from inflammation. This includes:

* Protecting yourself from viruses such as hepatitis B, hepatitis C and HIV.
* Limiting the amount of alcoholic beverages you drink.
* Maintaining a healthy body weight.
* Quitting smoking.

## 

### **What questions should I ask my healthcare provider?**

Questions to ask include:

## What type of cholangiocarcinoma do I have?

Cholangiocarcinoma is classified by its location in the bile ducts:

* Intrahepatic (iCCA): Occurs within the liver.
* Perihilar (pCCA): Occurs at the hilum, where the left and right bile ducts join (also called Klatskin tumor).
* Distal (dCCA): Occurs in the bile duct outside the liver, closer to the small intestine.  
  Your doctor will determine the type based on imaging and pathology.

## What is the stage of the cancer?

Staging depends on tumor size, location, involvement of blood vessels, lymph nodes, and whether it has spread to other organs. Imaging tests (CT, MRI) and sometimes surgical exploration are used for staging. The stage helps guide treatment and prognosis.

## What treatments would you recommend?

Treatment depends on the type, stage, and your overall health:

* Surgery: If the tumor is localized and you are a candidate, surgical removal offers the best chance for cure.
* Liver transplantation: May be considered in select early-stage perihilar cases.
* Chemotherapy: Often used if the cancer cannot be fully removed or has spread; gemcitabine and cisplatin are common drugs.
* Radiation therapy: Sometimes used after surgery or for symptom control.
* Locoregional therapies: Such as ablation or embolization, may be options in certain cases.

## Do I need biomarker testing?

Yes, biomarker and molecular testing are increasingly recommended for cholangiocarcinoma. These tests can identify genetic changes (such as FGFR2 fusions, IDH1/2 mutations) that may open up targeted therapy options or clinical trials.

## Are there clinical trials I can take part in?

Clinical trials are available for many patients with cholangiocarcinoma, especially for advanced or unresectable disease. Trials may offer access to new drugs, targeted therapies, or immunotherapies. Your doctor can review current trials and eligibility.

## What treatment side effects should I expect?

* Surgery: Pain, infection, bleeding, and possible liver dysfunction.
* Chemotherapy: Fatigue, nausea, lowered immunity, hair loss, and risk of infection.
* Radiation: Fatigue, skin changes, and possible effects on nearby organs.
* Targeted therapies: Side effects depend on the drug but may include diarrhea, fatigue, and skin changes.  
  Your care team will discuss side effects specific to your treatment plan.

## Is there anything I can do to make treatment more effective?

* Follow your treatment plan closely and attend all appointments.
* Maintain good nutrition and stay physically active as tolerated.
* Report side effects early so they can be managed.
* Avoid alcohol and substances that can further damage your liver.
* Ask about supportive care services (nutrition, physical therapy, counseling).

## How likely is it that cholangiocarcinoma will come back after treatment?

Cholangiocarcinoma has a high risk of recurrence, even after successful surgery, especially in advanced stages. The likelihood of recurrence depends on the stage at diagnosis, whether the cancer was completely removed, and other factors. Regular follow-up with imaging and blood tests is essential for early detection of recurrence.

**DIFFERENTIAL DIAGNOSIS**

Since the signs and symptoms of cholangiocarcinoma, including jaundice, abdominal pain, and fatigue, are very nonspecific, the differential diagnosis can be vast. Some possible differential diagnoses include:

* Choledocholithiasis
* Pancreatic cancer
* Primary sclerosing cholangitis
* Primary biliary cirrhosis
* Hepatocellular carcinoma
* Cholangitis
* Cholecystitis

**EPIDEMIOLOGY**

Cholangiocarcinomas comprise about 3% of gastrointestinal malignancies, are the second most common primary liver tumors, and account for approximately 10% to 15% of all hepatobiliary malignancies. The incidence of intrahepatic cholangiocarcinoma has been rising, possibly due to improved diagnostic and classification techniques, while the incidence of extrahepatic lesions has been falling in recent years. The incidence of cholangiocarcinoma varies markedly according to the geographic area; the incidence rates are up to 50-fold higher in parts of Thailand than in the United States. The incidence of cholangiocarcinoma increases with age, is slightly more common in men, and is most commonly diagnosed between the ages of 50 and 70 years.

Perihilar cholangiocarcinoma is the most commonly encountered subtype, accounting for approximately 50% of cases. Distal (40%) and intrahepatic cholangiocarcinoma (10%) are less common

## **Most Common Genomic Alterations**

* TP53:  
  One of the most frequently mutated genes in CCA, especially in liver fluke-associated and Asian cases (mutation rates up to 44%).
* KRAS:  
  Commonly mutated, especially in extrahepatic CCA (up to 43%) and perihilar tumors; also seen in intrahepatic CCA (8–54%).
* IDH1/2:  
  Mutations are more prevalent in intrahepatic CCA (10–20%), less common in extrahepatic tumors (2–3%).
* FGFR2 Fusions:  
  Found in 7–16% of intrahepatic CCA, especially in fluke-negative cases, and are actionable targets for therapy.
* SMAD4, ARID1A, BAP1, PBRM1:  
  Frequently altered in both intrahepatic and extrahepatic subtypes, with ARID1A and SMAD4 more common in fluke-positive tumors and BAP1, PBRM1, and IDH1/2 in fluke-negative cases.
* ERBB2 (HER2):  
  Amplifications and mutations are seen in both intrahepatic (8%) and extrahepatic (5–9%) CCA.
* PIK3CA, BRCA1/2:  
  Mutations occur in a minority of cases (PIK3CA: 5–7%, BRCA1: 0.4%, BRCA2: 2.7%).
* Other Notable Genes:
  + METTL14, RBM10: Mutated in perihilar CCA.
  + GNAS, MLL3, ROBO2, RNF43, TGFBR2, NF1: Additional recurrent mutations, especially in Asian and fluke-positive cases

### **Staging**

Cholangiocarcinoma cancer staging follows the tumor-node-metastasis (TNM) classification of the American Joint Cancer Committee/Union for International Cancer Control/ (AJCC/UICC) and is staged separately for intrahepatic, perihilar, and distal bile duct tumors.

TNM groupings by stage are as follows for each group:

Table.

| Intrahepatic bile duct tumor | | | |
| --- | --- | --- | --- |
| Stage | T | N | M |
| 0 | Tis | N0 | M0 |
| IA | T1a | N0 | M0 |
| IB | T1b | N0 | M0 |
| II | T2 | N0 | M0 |
| IIIA | T3 | N0 | M0 |
| IIIB | T4 | N0 | M0 |
|  | Any T | N1 | M0 |
| IV | Any T | Any N | M1 |

Table. 2

| Perihilar bile duct tumor | | | |
| --- | --- | --- | --- |
| Stage | T | N | M |
| 0 | Tis | N0 | M0 |
| I | T1 | N0 | M0 |
| II | T2a-b | N0 | M0 |
| IIIA | T3 | N0 | M0 |
| IIIB | T4 | N0 | M0 |
| IIIC | Any T | N1 | M0 |
| IVA | T4 | N2 | M0 |
| IVB | Any T | Any N | M1 |

Table. 3

| Distal bile duct tumor | | | |
| --- | --- | --- | --- |
| Stage | T | N | M |
| 0 | Tis | N0 | M0 |
| I | T1 | N0 | M0 |
| IIA | T1 | N1 | M0 |
|  | T2 | N0 | M0 |
| IIB | T2 | N1 | M0 |
|  | T3 | N0 | M0 |
|  | T3 | N1 | M0 |
| IIIA | T1-3 | N2 | M0 |
| IIIB | T4 | N0-2 | M0 |
| IV | Any T | Any N | M1 |

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### Treatment

For intrahepatic and extrahepatic cholangiocarcinomas resected with microscopic margins or positive regional nodes, options include the following:

* Systemic therapy (preferred)
* Fluoropyrimidine-based chemoradiation
* Fluoropyrimidine- or gemcitabine-based chemotherapy followed by fluoropyrimidine-based chemoradiation
* Fluoropyrimidine-based chemoradiation followed by fluoropyrimidine- or gemcitabine-based chemotherapy

## **Doctor-Patient Conversation: Cholangiocarcinoma (Bile Duct Cancer)**

Doctor: Thank you for coming in today. I have your test results, and I’d like to talk through them with you. The diagnosis is cholangiocarcinoma, which is a cancer of the bile ducts.

Patient: What exactly is cholangiocarcinoma, and how was it diagnosed?

Doctor: Cholangiocarcinoma is a rare cancer that starts in the bile ducts, which are tubes that carry bile from your liver to your intestines. We diagnosed it based on your symptoms, blood tests, and imaging scans. A biopsy confirmed the diagnosis.

Patient: What type of cholangiocarcinoma do I have?

Doctor: There are three main types, depending on where the tumor is located:

* Intrahepatic (inside the liver)
* Perihilar (at the junction where the left and right bile ducts meet)
* Distal (closer to the small intestine)  
  Your imaging and biopsy results show that you have [doctor specifies type] cholangiocarcinoma.

Patient: What stage is my cancer?

Doctor: The stage depends on the size of the tumor, whether it has spread to lymph nodes or other organs, and your overall health. We use imaging studies and sometimes additional tests to determine the stage. This helps us decide on the best treatment plan for you.

Patient: What are my treatment options?

Doctor: Treatment depends on the type, stage, and your general health. If the tumor is localized and you are a good candidate, surgery to remove the tumor offers the best chance for cure. If surgery isn’t possible, other options include chemotherapy, targeted therapy, radiation, or procedures to relieve symptoms like jaundice. We’ll discuss these options in detail and tailor the plan to your needs.

Patient: Should I have biomarker or genetic testing?

Doctor: Yes, biomarker and molecular testing are often recommended. These tests can identify genetic changes in the tumor that may help us choose targeted therapies or clinical trials that are best suited for you.

Patient: Are there clinical trials available?

Doctor: There are clinical trials for cholangiocarcinoma, especially for advanced cases or when standard treatments are not effective. We can discuss whether you might be eligible for any ongoing trials and what they involve.

Patient: What side effects should I expect from treatment?

Doctor: Side effects depend on the treatment. Surgery can cause pain and risk of infection. Chemotherapy may cause fatigue, nausea, and lowered immunity. Targeted therapies and radiation have their own specific side effects, which we’ll review before you start any treatment.

Patient: Is there anything I can do to help my treatment work better?

Doctor: Staying as healthy as possible, following your treatment plan, reporting any side effects early, and keeping up with follow-up appointments can all help. Good nutrition, physical activity as tolerated, and support from friends or family are also important.

Patient: How likely is it that the cancer will come back after treatment?

Doctor: Cholangiocarcinoma has a risk of recurrence, especially if it’s diagnosed at a later stage. The risk depends on the stage at diagnosis, the success of surgery, and other factors. We’ll monitor you closely with regular check-ups and scans after treatment.

Patient: Thank you for explaining everything.

Doctor: You’re welcome. Please write down any questions you have, and bring them to our next visit. We’re here to support you every step of the way.

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### **Non-small cell lung cancer**

Non-small cell lung cancer (NSCLC) occurs when abnormal cells form and multiply in your lungs. NSCLC is one of two main types of lung cancer. The other is small cell lung cancer (SCLC). NSCLC is the most common type of lung cancer, making up about 80% to 85% of all lung cancer cases.

Small cell lung cancer gets its name because the cancer cells look small and round under a microscope. Generally, SCLC is more aggressive than NSCLC. With non-small cell lung cancer, the cancer cells are larger, and they typically grow slower.

NSCLC may not cause symptoms. So, even though it grows slower than small cell, it’s often diagnosed after the cancer has spread (metastasized) to other areas of your body. That’s why early detection and treatment are so important.

### **Types of non-small cell lung cancer**

There are three main types of non-small cell lung cancer:

1. Adenocarcinoma: Usually forms in the outer portions of your lung
2. Large cell carcinoma: Can develop in any part of your lungs
3. Squamous cell carcinoma: Typically starts in the central part of your lungs

Other types of non-small cell lung cancer include sarcomatoid carcinoma and adenosquamous carcinoma. They’re much less common.

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### **Symptoms of non-small cell lung cancer**

Non-small cell lung cancer symptoms can include:

* Chest pain
* Chronic cough
* Coughing up blood
* Hoarseness
* Loss of appetite
* Shortness of breath
* Tiredness
* Wheezing

In some cases, NSCLC may not cause symptoms.

### **Non-small cell lung cancer causes**

NSCLC occurs when normal cells change and grow out of control. But experts don’t always know why it happens in some people and not in others. But they have identified some risk factors. A risk factor is something that increases your chances of developing non-small cell lung carcinoma.

#### **Risk factors**

The most common risk factor for lung cancer is a history of smoking. Other known NSCLC risk factors include:

* A family history of lung cancer
* Asbestos exposure
* Exposure to metal and mineral dust
* Exposure to radon, a naturally occurring radioactive gas
* Having respiratory conditions like pulmonary fibrosis or COPD
* Radiation therapy to your breast or chest

### **Complications of non-small cell lung cancer**

Like many other cancers, non-small cell lung cancer can spread to other parts of your body. Most commonly, it can spread to your:

* Adrenal glands
* Bones
* Brain
* Liver
* Lymph nodes
* Skin

## **Diagnosis and Tests**

Your healthcare provider will do a physical examination and ask about your symptoms and medical history. If they suspect non-small cell lung cancer, they’ll recommend certain tests to diagnose and stage the disease.

#### **Tests that are used**

Medical tests that help diagnose non-small cell lung cancer include:

* Lung biopsy
* Bronchoscopy, which gives your healthcare provider a view inside your airways
* Imaging tests like chest X-rays or CT scans, PET scans and MRI scans of the brain
* Video-assisted thoracic surgery (VATS), which helps your provider get a better look inside your chest

## **Management and Treatment**

For cancer that’s only in your lung and nowhere else, your healthcare provider may recommend surgery as a first line of treatment. During this procedure, a surgeon removes the tumor and a small amount of healthy tissue around it. If the cancer has spread beyond the original site, all or part of your lung may need to be removed (lung resection).

Early-stage lung cancer is rare, so many people receive a combination of treatments, including:

* Chemotherapy. Chemotherapy involves using drugs that attack lung cancer. It’s one of the most common NSCLC treatments. Your oncologist might recommend chemotherapy on its own or in combination with other therapies.
* Immunotherapy. This treatment uses certain drugs to boost your immune system so it can recognize and destroy cancer cells.
* Targeted therapy. This treatment uses drugs designed for specific types of lung cancer. Targeted therapy can find and attack specific cancer cells without harming healthy cells.
* Radiation therapy. A radiation specialist uses X-rays to kill cancer by carefully aiming them at the lung cancer wherever it is in your body. Your provider might use it in combination with chemotherapy or on its own.

### **Recovery time**

Recovery after non-small cell lung cancer treatment varies. It depends on several factors like the size and location of the tumor, the type of treatment you receive and your body’s own healing capacity.

Some people may recover in a few months. For others, it might take years. Ask your healthcare provider what you can expect in your situation.

### **When should I see my healthcare provider?**

See your oncologist or visit your nearest emergency room if you develop:

* Breathing problems
* Fever of 100.4 degrees Fahrenheit (38 degrees Celsius)
* Severe pain that doesn’t improve with medication
* New or worsening symptoms

## **Outlook / Prognosis**

Life expectancy depends on the stage of cancer and the subtype of NSCLC. For example, the five-year survival rate for early-stage NSCLC is 65%. This means that 65% of people diagnosed with the condition are still alive five years later.

The five-year survival rate for regional NSCLC (when the cancer has spread to nearby tissues or lymph nodes) is 37%. With metastatic non-small cell lung cancer, the five-year survival rate is 9%.

Keep in mind that survival rates are just estimates. They can’t tell you how long you’ll live or how your body will respond to treatment. To learn more about what survival rates mean for you, talk to your healthcare provider.

And the outlook is different for everyone. Non-small cell lung cancer may be curable, especially with early detection and treatment. But certain factors affect your overall prognosis, like cancer type, stage and your overall health.

Even when NSCLC isn’t curable, it’s still treatable in many cases. Many people with non-small cell lung cancer can manage their symptoms successfully.

## **Epidemiology**

### United States statistics

In the United States, lung cancer is the second most common cancer, after prostate cancer in men and breast cancer in women, but the most common cause of cancer deaths. The American Cancer Society projects that 226,650 cancers of the lung and bronchus will be diagnosed in the United States in 2025, with 124,730 deaths. Approximately 87% of those cases are expected to be NSCLC.

Incidence rates of lung cancer follow those of tobacco smoking, with a lag of several decades. Because women took up cigarette smoking in large numbers later and were slower to quit, declines began later and have been slower in women than in men. The incidence rate of lung cancer in men has been decreasing since the mid-1980s, but the rate in women did not begin to fall until the mid-2000s. From 2012 to 2021, the incidence rate of lung cancer declined by 3.0% per year in men and by 1.4% per year in women.

Lung cancer death rates in the US fell on average 4.2% each year over 2014–2023, decreasing from 43.8 to 29.4 per 100,000 population during that period.This reduction outpaces declines in incidence and likely reflects advances in treatment, as well as earlier detection, facilitated by lung cancer screening, which has been recommended for persons at high risk for lung cancer since 2013.

### International statistics

Lung cancer is the second most commonly diagnosed cancer worldwide, after breast cancer, and its incidence continues to grow. In 2022, an estimated 2.5 million new cases of lung cancer were diagnosed globally, accounting for approximately 12.4% of the global cancer burden. An estimated 1.8 million lung cancer deaths occurred in 2022.Among all cancers, lung cancer is currently the most common cause of cancer deaths in most countries, with industrialized regions such as Eastern Asia, North America, and Europe having the highest rates.

Several differences exist in lung cancer incidence according to geographic area. The highest incidence occurs in Eastern Asia (39.4 cases per 100,000 population per year). The lowest incidence rate is in western Africa (approximately 2.1 cases per 100,000 population per year).With increased smoking in developing countries, the incidence is expected to increase in the next few years, notably in China and India.

Generally, global lung cancer trends have followed the trends in smoking, with a lag time of several decades. Lung cancer incidence has been declining in several countries, including the United States, Canada, the United Kingdom, and Australia, following the decreasing rate of smoking. Lung cancer incidence among women, however, continues to increase in several parts of the globe, although it has begun to plateau in the United States. Notably, despite a very low rate of smoking, Chinese women have a higher incidence of lung cancer than European women.

### Age and sex distribution

Lung cancer occurs predominantly in persons aged 50-70 years. The probability of developing lung cancer remains very low until age 39 years in both sexes. It then slowly starts to rise and peaks among those older than 70 years. The risk of developing lung cancer remains higher among men in all age groups after age 40 years.

Overall, lung cancer is more common in men than in women. In the United States, Northern Europe, and Western Europe, the prevalence of lung cancer has been decreasing in men. In Eastern and Southern European countries, the incidence of lung cancer has been rapidly increasing. Most Western countries have encountered a disturbing trend of increasing prevalence in women and younger patients. Women have a higher incidence of localized disease at presentation and of adenocarcinoma and typically are younger when they present with symptoms.

Over the past two decades, the incidence of lung cancer has generally decreased in both men and women 30 to 54 years of age in all races and ethnic groups. However, the incidence has declined more steeply in men. As a result, lung cancer rates in younger women have become higher than those in younger men. In non-Hispanic whites and Hispanics ages 44 to 49 years, for example, the female-to-male rate ratio for lung cancer incidence rose from 0.88 during 1995-1999 to 1.17 during 2010-2014.

This reversal can be explained in part by increased rates of cigarette smoking in women born since 1965. However, while the difference in smoking rates in that age group has narrowed, rates in women have generally not exceeded the rates in men, so other factors may be playing a role. For example, women may be more susceptible to the oncogenic effects of smoking.

### Incidence and survival by race

In men, lung cancer incidence rates are higher in Blacks than in Whites (65.2 vs 58.2 cases per 100,000 population), while in women, incidence rates are higher in Whites than in Blacks (51.2 vs 43.1 per 100,000 population); lung cancer death rates follow the same pattern.Those differences have been attributed to differences in smoking habits; however, recent evidence suggests a slight difference in susceptibility.

National 5-year survival rates are estimated to be 18% in Whites and 15% in Blacks, but Blacks are more likely than WhItes to be diagnosed at late stage disease and are less likely to receive the recommended stage-based treatment. Controlling for stage and socioeconomic factors has been shown to eliminate the difference in survival between Blacks and Whites.

## **Diagnostic Considerations**

Non–small cell lung cancer (NSCLC) must be differentiated from small cell lung cancer (SCLC) in order to plan appropriate treatment. SCLC is usually more aggressive than NSCLC and presents as a central lesion with hilar and mediastinal invasion along with regional adenopathy. Many patients with SCLC already have metastatic disease at initial diagnosis. The most common sites of metastasis of lung cancer are the bones, liver, adrenal glands, pericardium, brain, and spinal cord.

Other conditions to be considered include the following:

* Benign lung tumors
* Carcinoid lung tumors
* Granuloma
* Hamartoma
* Metastatic cancer
* Pneumomediastinum
* Pneumonia, empyema, and abscess
* Pneumothorax, tension and traumatic

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## **Staging**

The most important prognostic indicator in lung cancer is the extent of disease and lymph node involvement. The American Joint Committee for Cancer Staging and End Results Reporting has developed the TNM (tumor-node-metastasis) staging system, which takes into account the degree of spread of primary tumor, the extent of regional lymph node involvement, and the presence or absence of distant metastases (see the table below).The TNM system is used for all lung carcinomas except SCLCs.

### AJCC TNM staging and grouping system

Primary tumor (T) involvement is as follows:

* TX - Primary tumor cannot be assessed
* T0 - No evidence of primary tumor
* Tis - Carcinoma in situ; squamous cell carcinoma in situ; adenocarcinoma in situ; adenocarcinoma with pure lepidic pattern, 3 cm or less in greatest dimension
* T1 - Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (not in the main bronchus)
* T1mi - Minimally invasive adenocarcinoma: adenocarcinoma (3 cm or less in greatest dimension) with a predominantly lepidic pattern and 5 mm or less invasion in greatest dimension
* T1a - Tumor 1 cm or less in greatest dimension
* T1b - Tumor more than 1 cm but 2 cm or less
* T1c - Tumor more than 2 cm but 3 cm or less
* T2 - Tumor more than 3 cm but 5 cm or less, or one with any of the following features:(1) Involves the main bronchus, regardless of distance to the carina, but without involvement of the carina; (2) Invades visceral pleura (PL1 or PL2); (3) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
* T2a - Tumor more than 3 cm but 4 cm or less
* T2b - Tumor more than 4 cm but 5 cm or less
* T3 - Tumor more than 5 cm but 7 cm or less, or one that invades any of the following: : parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary
* T4 - Tumor more than 7 cm, or of any size that invades one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

Lymph node (N) involvement is as follows:

* NX - Regional nodes cannot be assessed
* N0 - No regional node metastasis
* N1 - Metastasis in ipsilateral peribronchial and/or ipsilateral hilar nodes and intrapulmonary nodes, including involvement by direct extension
* N2 - Metastasis in ipsilateral mediastinal and/or subcarinal node
* N3 - Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene node, or supraclavicular node

Metastatic (M) involvement is as follows:

* MX - Distant metastasis cannot be assessed
* M0 - No distant metastasis
* M1 - Distant metastasis
* M1a - Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion
* M1b - Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
* M1c - Multiple extrathoracic metastases in one or more organs

AJCC prognostic groups for NSCLC comprise 4 stages, with further subdivision of stages into subtypes. These stages have important therapeutic and prognostic implications, which are discussed later.

Stage grouping of the TNM system is as follows:

* Stage 0 - TisN0M0
* Stage IA1- T1miN0M0 / T1aN0M0
* Stage IA2 - T1bN0M0
* Stage IA3 - T1cN0M0
* Stage IB - T2aN0M0
* Stage IIA - T2bN0M0
* Stage IIB - T1aN1M0 / T1bN1M0 / T1cN1M0 / T2aN1M0 / T2bN1M0 / T3N0M0
* Stage IIIA - T1aN2M0 / T1bN2M0 / T1cN2M0 / T2aN2M0 / T2bN2M0 /T3N1M0 / T4N0M0 / T4N1M0
* Stage IIIB - T1aN3M0 / T1bN3M0 / T1cN3M0 / T2aN3M0 / T2bN3M0 / T3N2M0 / T4N2M0
* Stage IIIC - T3N3M0 / T4N3M0
* Stage IVA - Any T, any N, M1a or M1b
* Stage IVB - Any T, any N, M1c
* M1a designates metastasis within the thoracic cavity
* M1b designates a single extrathoracic metastasis
* M1c designates multiple extrathoracic metastases

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### **Outline of treatment options by stage**

Treatment of NSCLC by stage is as follows:

* Stage IA - Surgery only; no adjuvant chemotherapy
* Stage IB-IIIA - Surgery followed by adjuvant chemotherapy with four cycles of a cisplatin-based regimen and, in cases with an *EGFR* exon 19 deletion or exon 21 L858R mutation, adjuvant osimertinib
* Stage II-IIIB - If surgically unresectable, chemoradiation plus durvalumab for one year if chemoradiation results in a partial or complete response
* Stage IV - Treat on the basis of histology (squamous or non-squamous) and molecular profile and biomarkers

Treatment of stage IV squamous NSCLC is as follows:

* Cisplatin-based chemotherapy
* If programmed death ligand 1 (PD-L1) expression is 1-49%, chemotherapy plus pembrolizumab
* If PD-L1 expression is > 50%, pembrolizumab alone

Treatment of stage IV non-squamous NSCLC is as follows:

* If PD-L1 expression is 1-49%, cisplatin-based chemotherapy plus pembrolizumab
* If PD-L1 expression is > 50%, pembrolizumab alone
* Cisplatin-based chemotherapy plus bevacizumab is also a reasonable option
* Oral tyrosine kinase inhibitor or other targeted therapy for tumors with treatable driver mutations (eg, *EGFR, ALK, ROS1, RET, BRAF,NTRK* gene fusion, *MET* exon 14 skipping;

### **Emergency treatment**

All patients thought to have lung cancer should be encouraged to obtain follow-up care with their primary care physician. In almost all cases, document the possible diagnosis and discuss it with the patient. Definitive treatment of the underlying cancer is not the purview of the emergency department (ED).

Emergency treatment is based on symptoms. In cases of upper airway obstruction, admit the patient to the intensive care unit (ICU), prepare for intubation and/or cricothyrotomy, and obtain otolaryngologic and/or surgical consultation for fiberoptic laryngoscopy or intraoperative tracheostomy.

If hemoptysis is noted, administer supplemental oxygen and perform suctioning. If a threat of imminent demise exists, consider placing a double-lumen endotracheal tube. Position the patient with the bleeding hemithorax in a dependent position. Perform arterial blood gas (ABG) and complete blood count (CBC) (type and crossmatching) coagulation studies if the bleeding is more than trivial. A pulmonologist may have to perform fiberoptic bronchoscopy. Admit patients, except those with the most minor bleeding, to the ICU.

## **Antineoplastic Agents**

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Antineoplastic agents are used either to prolong survival or to palliate symptoms in advanced or unresectable lung cancer.

## Carboplatin

Carboplatin has a mechanism of action similar to that of cisplatin. It is approved for ovarian cancer but is used commonly in squamous cell carcinoma (SCC) of the head, neck, cervix, and lungs. Its main advantages over cisplatin include less nephrotoxicity and ototoxicity (not requiring extensive prehydration) and reduced likelihood of inducing nausea and vomiting. It is more likely to induce myelotoxicity.

## 

## Vinorelbine (Navelbine)

Vinorelbine is a semisynthetic vinca alkaloid that inhibits tubulin polymerization during the G2 phase of cell division, thereby inhibiting mitosis. Vinorelbine alone or in combination with cisplatin is indicated as first-line treatment of ambulatory patients with unresectable, advanced NSCLC and for stage IV NSCLC. In stage III NSCLC, vinorelbine is indicated in combination with cisplatin.

## 

## Paclitaxel (Taxol)

Paclitaxel is a naturally occurring chemical derived from the Pacific yew tree (Taxus brevifolia). It inhibits tubulin depolymerization in the spindle during cell division. Paclitaxel is used in combination with cisplatin for the first-line treatment of NSCLC in patients who are not candidates for potentially curative surgery or radiation therapy.

## 

## Paclitaxel protein bound (Abraxane)

Protein-bound paclitaxel is a microtubular inhibitor (albumin-conjugated formulation). It is a natural taxane, and it prevents depolymerization of cellular microtubules, which results in DNA, RNA, and protein synthesis inhibition. It is indicated for locally advanced or metastatic NSCLC, as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

## 

## Cisplatin

Cisplatin is an alkylating agent that causes intrastrand and interstrand cross-linking of DNA, leading to strand breakage. It has a very broad range of antitumor activity and is approved for use in testicular, ovarian, and transitional cell carcinomas. It forms the basis of currently available approved combination chemotherapy regimens for NSCLC. Administer it as a single-dose intravenous (IV) infusion or in divided doses over several days; this can be repeated only after complete hematologic recovery; cycles are typically separated by 3-4 wk.

## 

## Gemcitabine (Gemzar, Infugem)

Gemcitabine is an antimetabolite that acts as an inhibitor of DNA synthesis. It is cell-cycle specific for the S phase. Gemcitabine is used as first-line treatment of patients with inoperable, locally advanced (stage IIIA or IIIB), or metastatic (stage IV) NSCLC in combination with cisplatin.

## 

## Docetaxel (Docefrez, Taxotere)

Docetaxel is a semisynthetic taxane, a class of drugs that inhibits cancer cell growth by promoting assembly and blocking disassembly of microtubules, thereby preventing cancer cell division, leading to cell death. It is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy when used alone. It can be used in combination with cisplatin for the treatment of patients with unresectable, locally advanced, or metastatic NSCLC who have not previously received chemotherapy for this condition.

## 

## **Pemetrexed (Alimta, Pemfexy, Pemrydi)**

Pemetrexed disrupts folate-dependent metabolic processes essential for cell replication. It specifically inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in de novo biosynthesis of thymidine and purine nucleotides. It is indicated for nonsquamous NSCLC as follows:

1) Initial treatment in combination with pembrolizumab and platinum chemotherapy for patients with metastatic disease with no EGFR or ALK genomic tumor aberrations

2) Initial treatment in combination with cisplatin for patients with locally advanced or metastatic disease

3) Single agent for maintenance in patients with locally advanced or metastatic disease that has not progressed after 4 cycles of platinum-based first-line chemotherapy

4) Single agent for treatment of patients with recurrent metastatic disease after prior therapy

## Cyclophosphamide (Cytoxan)

Cyclophosphamide is chemically related to nitrogen mustards; as an alkylating agent, the mechanism of action of active metabolites may involve cross-linking of DNA, which may interfere with growth of normal and neoplastic cells.

## Doxorubicin (Adriamycin, Caelyx, Rubex)

Doxorubicin is an anthracycline that inhibits topoisomerase II and produces free radicals, which may cause destruction of DNA; the combination of these 2 events can, in turn, inhibit the growth of neoplastic cells.

## Vincristine

Vincristine is a vinca alkaloid whose mechanism of action is uncertain. It may involve a decrease in reticuloendothelial cell function or an increase in platelet production. However, neither of these mechanisms fully explains the effect in thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. The antineoplastic effects of vincristine are related to its binding to tubulin and inhibition of microtubule formation.

## Etoposide (Etopophos, Toposar, VePesid)

Etoposide inhibits topoisomerase II and causes DNA strand breakage, causing cell proliferation to arrest in the late S or early G2 portion of cell cycle; do not administer IT.

## **Antineoplastics, Anaplastic Lymphoma Kinase Inhibitors**

## 

Testing for ALK rearrangement is recommended in patients with metastatic NSCLC adenocarcinoma to determine if a therapy targeted toward ALK would be beneficial.

## Crizotinib (Xalkori)

Inhibitor of receptor tyrosine kinases including, anaplastic lymphoma kinase (ALK), hepatocyte growth factor receptor (HGFR, c-Met), and recepteur d'origine nantais (RON). The gene's expression and signaling that contribute to increased cell proliferation and survival of the tumors becomes activated following the expression of ALK oncogenic fusion proteins. Indicated for locally advanced or metastatic non-small cell lung cancer (NSCLC) that is ALK positive as detected by an FDA-approved test. It is also indicated for NSCLC tumors positive for the ROS-1 gene mutation.

## Ceritinib (Zykadia)

Ceritinib is a tyrosine kinase inhibitor that targets anaplastic lymphoma kinase (ALK), insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS1. It is indicated for ALK-positive, metastatic NSCLC.

## Alectinib (Alecensa)

* [View full drug information](https://reference.medscape.com/drug/alecensa-alectinib-1000067)

Tyrosine kinase inhibitor that targets ALK and RET. The major active metabolite of alectinib, M4, showed similar in vitro potency and activity. In nonclinical studies, alectinib inhibited ALK phosphorylation and ALK-mediated activation of the downstream signaling proteins STAT3 and AKT, and decreased tumor cell viability in multiple cell lines harboring ALK fusions, amplifications, or activating mutations.. It is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic NSCLC as detected by an FDA-approved test.

## Brigatinib (Alunbrig)

Brigatinib inhibits autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signaling proteins STAT3, AKT, ERK1/2, and S6 in in vitro and in vivo assays. It is indicated for ALK-positive metastatic NSCLC in patients who have progressed on or are intolerant to crizotinib.

## Lorlatinib (Lorbrena)

ALK/ROS1 tyrosine kinase inhibitor indicated for ALK-positive metastatic NSCLC

## Ensartinib (Ensacove)

ALK tyrosine kinase inhibitor; also inhibits other TKIs (eg, MET and ROS1). Blocks ALK-mediated signaling pathways and downstream signaling proteins (eg, AKT, ERK, and S6) by inhibiting ALK

## **PD-1/PD-L1 Inhibitors**

PD-1 and related target PD-ligand 1 (PD-L1) are expressed on the surface of activated T cells. Under normal conditions, PD-L1/PD-1 interaction inhibits immune activation and reduces T-cell cytotoxic activity when bound. This negative feedback loop is essential for maintaining normal immune responses and limits T-cell activity to protect normal cells during chronic inflammation. Tumor cells may circumvent T-cell–mediated cytotoxicity by expressing PD-L1 on the tumor itself or on tumor-infiltrating immune cells, resulting in the inhibition of immune-mediated killing of tumor cells; therefore, inhibiting the ligand binding will enhance T-cell mediated immune response.

## Nivolumab (Opdivo)

Monoclonal antibody to programmed cell death-1 protein (PD-1). It blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Restores cytokine secretion and T cell activity. It is indicated for metastatic squamous and nonsquamous (including adenocarcinoma) NSCLC with progression on or after platinum-based chemotherapy. It is also indicated, in combination with ipilimumab, for metastatic NSCLC in patients whose tumors express PD-L1 (≥1%), with no EGFR or ALK tumor aberrations; and, in combination with ipilimumab and two cycles of platinum-doublet chemotherapy, for the first-line treatment of metastatic or recurrent NSCLC in patients whose tumors have no EGFR or ALK aberrations, regardless of PD-L1 expression. In addition to metastatic NSCLC, it is also indicated for resectable (tumors ≥4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy.

## Pembrolizumab (Keytruda)

Pembrolizumab is a monoclonal antibody to programmed cell death-1 protein (PD-1). It blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. It is indicated as a single agent for first-line treatment of patients with stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC whose tumors express PD-L1 (Tumor Proportion Score [TPS] ≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations. Pembrolizumab is also indicated as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy; patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.

Pembrolizumab is indicated in combination with pemetrexed and carboplatin for first-line treatment of patients with metastatic nonsquamous NSCLC irrespective of PD-L1 expression. It is also indicated first-line in combination with carboplatin and either paclitaxel or nab-paclitaxel for patients with metastatic squamous NSCLC.

## Atezolizumab (Tecentriq)

Atezolizumab is a monoclonal antibody to PD-L1. It is indicated as single-agent therapy following resection and platinum-based chemotherapy for adults with stage II to IIIA NSCLC whose tumors have PD-L1 expression ≥ 1%; for first-line treatment of metastatic NSCLC whose tumors have high PD-L1 expression with no EGFR or ALK genomic tumor aberration; and for second-line treatment of metastatic NSCLC that progresses during or after platinum-containing chemotherapy. It is also indicated in combination with bevacizumab, paclitaxel, and carboplatin, or in combination with paclitaxel protein-bound and carboplatin, for first-line treatment of patients with metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations.

## Durvalumab (Imfinzi)

Human IgG1 kappa monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80, and therefore overcoming/preventing PD-L1-mediated inhibition/suppression of T-cell activation. It is indicated for unresectable, Stage III NSCLC in patients whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

Also indicated in combination with tremelimumab and platinum-based chemotherapy for adults with metastatic NSCLC with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

## Cemiplimab (Cemiplimab-rwlc, Libtayo)

Cemiplimab is a recombinant human IgG4 monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L1, releasing the PD-1 pathway-mediated inhibition of the immune response, including antitumor immune response, thereby decreasing tumor growth. Binding of the PD-1 ligands PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. It is approved for first-line treatment of NSCLC whose tumors have high PD-L1 expression [TPS ≥50%] with no EGFR, ROS-1, or ALK mutations.

## Ipilimumab (Yervoy)

Recombinant, human cytotoxic T-lymphocyte antigen. Proposed mechanism of action is indirect, possibly through inhibition of CTLA-4 signaling, which can in turn reduce T-regulatory cell function and may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response. It is indicated in combination with nivolumab, for metastatic NSCLC in patients whose tumors express PD-L1 (≥1%), with no EGFR or ALK tumor aberrations.

## Atezolizumab/hyaluronidase (Atezolizumab/hyaluronidase-tqjs, Tecentriq Hybreza)

Monoclonal antibody that blocks programmed death-ligand 1 (PD-L1) from binding to programmed death-receptor 1 (PD-1) and B7.1 receptors. Product formulation of atezolizumab with hyaluronidase, an endoglycosidase, enables subcutaneous administration.

## **Anti-CTLA 4 Antibodies**

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocking monoclonal antibody blocks the interaction with its ligands CD80 and CD86. This action releases CTLA-4-mediated inhibition of T-cell activation.

## Tremelimumab (Imjudo, Tremelimumab-actl)

Indicated in combination with durvalumab for and platinum-based chemotherapy for adults with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic

## **Antineoplastics, EGFR Inhibitors**

## 

EGFR is expressed on the cell surface of both normal and cancer cells and plays a role in the processes of cell growth and proliferation.

## Osimertinib (Tagrisso)

EGFR kinase inhibitor, which binds irreversibly to certain mutant forms of EGFR (T790M, L858R, and exon 19 deletion). Osimertinib is indicated as first-line treatment for metastatic NSCLC in patients with EGFR exon 19 deletions or exon 21 L858R mutations as monotherapy or in combination with pemetrexed and platinum-based chemotherapy. Significant improvement was observed in the Phase 3 FLAURA2 trial that compared first-line combination treatment with monotherapy.

It is also indicated for metastatic EGFR T790M mutation–positive NSCLC in patients whose disease has progressed on or after EGFR TKI therapy. Additionally, it is indicated as adjuvant therapy after tumor resection in NSCLC patients whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations.

## Gefitinib (Iressa)

Gefitinib reversibly inhibits the kinase activity of wild-type and certain activating mutations of *EGFR*, preventing autophosphorylation of tyrosine residues associated with the receptor, thereby inhibiting further downstream signalling and blocking EGFR-dependent proliferation. It is indicated for the treatment of patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

## Erlotinib (Tarceva)

Erlotinib is pharmacologically classified as an HER1/EGFR tyrosine kinase inhibitor (TKI). EGFR is expressed on the cell surface of normal cells and cancer cells. It is approved for NSCLC in patients whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test for first-line treatment, maintenance treatment, or as second- or greater-line treatment after progression following at least 1 prior chemotherapy regimen. It also is indicated in combination with ramucirumab for first-line treatment of patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations.

## Afatinib (Gilotrif)

Afatinib covalently binds to the kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4) and irreversibly inhibits tyrosine kinase autophosphorylation, resulting in downregulation of ErbB signaling. It demonstrates inhibition of autophosphorylation and in vitro proliferation of cell lines expressing wild-type *EGFR* or those expressing selected *EGFR* exon 19 deletion mutations or exon 21 L858R mutations, including some with a secondary T790M mutations

Afatinib is indicated for first-line treatment of patients with metastatic NSCLC whose tumors have non-resistant *EGFR* mutations as detected by an FDA-approved test. Additionally, afatinib is indicated for first-line use in metastatic NSCLC for 3 additional nonresistant *EGFR* mutations (L861Q, G719X, S768I). It is also indicated for metastatic squamous NSCLC that has progressed after platinum-based chemotherapy.

## Dacomitinib (Vizimpro)

Irreversible kinase inhibitor of the human EGFR family (EGFR/HER1, HER2, and HER4) and certain EGFR-activating mutations (exon 19 deletion or the exon 21 L858R substitution mutation). It is indicated for first-line treatment of patients with metastatic NSCLC with *EGFR* exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test.

## Amivantamab (Amivantamab-vmjw, Rybrevant)

Bispecific antibody that binds to the extracellular domains of EGFR and MET; indicated for locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations, as detected by an FDA-approved test, in adults whose disease has progressed on or after platinum-based chemotherapy. It is administered as an IV infusion.

## Lazertinib (Lazcluze)

Indicated in combination with amivantamab for first-line treatment of locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations

## **Antineoplastics, Anti-HER2**

## 

Mutations in the gene encoding HER2 drive approximately 3% of nonsquamous NSCLCs and are associated with female sex, never-smoking history, and a poor prognosis, as well as with a slightly younger age and higher incidence of brain metastases than NSCLC without HER2 mutations or with other mutations.

## Trastuzumab deruxtecan (Enhertu, Fam-trastuzumab deruxtecan-nxki)

Indicated for unresectable or metastatic *HER2*-mutant NSCLC based on presence of activating *HER2* (ERBB2) mutations in tumor or plasma specimens in patients who have received prior systemic therapy.

## **Antineoplastics, BRAF Kinase Inhibitors**

## 

*BRAF* genes direct protein production which induces signal transmission along the RAS/MAPK pathway. RAS/MAPK pathway regulates cell growth, cell differentiation, cell migration, and apoptosis. *BRAF* mutations can cause dysregulation of cell growth, resulting in tumor progression [263]

## Dabrafenib (Tafinlar)

Dabrafenib selectively inhibits multiple mutated BRAF kinases, BRAF V600E, BRAF V600K, and BRAF V600D. BRAF kinase inhibition primarily stunts cells growth. The combination of dabrafenib with trametinib targets two different kinases in the RAS/MEK pathway, causing greater growth inhibition of tumors with the *BRAF* V600 mutation.

## Antineoplastics, Tyrosine Kinase Inhibitors

## Entrectinib (Rozlytrek)

Entrectinib and its major metabolite inhibit tropomyosin receptor tyrosine kinases (TRKs), proto-oncogene tyrosine-protein kinase ROS1 (ROS1), and anaplastic lymphoma kinase (ALK). It is indicated for metastatic NSCLC in adults whose tumors are ROS1-positive. Entrectinib is also indicated for NTRK genetic fusion solid tumors in pediatric and adult patients for whom there are no effective treatments.

## Larotrectinib (Vitrakvi)

Larotrectinib is an oral tyrosine kinase inhibitor that binds to tropomyosin receptor kinase (TrK), preventing TrK activation. This induces cellular apoptosis and inhibition of cell growth in tumors. It is currently indicated for solid tumors that have an *NTRK* gene fusion in adults and pediatric patients without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.

## Repotrectinib (Augtyro)

Indicated for adults with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC). Repotrectinib is an inhibitor of proto-oncogene tyrosine-protein kinase ROS1 (ROS1) and tropomyosin receptor tyrosine kinases (TRKs) TRKA, TRKB, and TRKC.

## **RET Kinase Inhibitors**

## 

Genomic alterations in rearranged during transfection (RET) kinase, which include fusions and activating point mutations, lead to overactive RET signaling and uncontrolled cell growth.

## Selpercatinib (Retevmo)

Selpercatinib is a kinase inhibitor of wild-type rearranged during transfection (RET) and multiple mutated RET isoforms, as well as vascular endothelial growth factor receptors (VEGFR1, VEGFR3). It is indicated for metastatic RET fusion-positive NSCLC.

## Pralsetinib (Gavreto)

Pralsetinib is a selective inhibitor of RET alterations and resistant mutations; specifically designed to spare VEGFR2 and other kinases with the potential to drive off-target toxicity. This RET inhibitor exhibited antitumor activity in cultured cells and animal tumor implantation models harboring oncogenic RET fusions or mutations. It is Indicated for metastatic RET gene-positive NSCLC.

## **MET Tyrosine Kinase Inhibitors**

Mitogen extracellular signal-regulated kinase (MEK) protein acts downstream from Ras in the mitogen-activated protein kinase (MAPK) pathway. MAPK pathway regulates cell growth, cell differentiation, cell migration, and apoptosis. Blockage of MEK protein may affect tumors with mutated Ras proteins or other proteins influenced by MAPK pathway.

## Capmatinib (Tabrecta)

Capmatinib is a kinase inhibitor that targets mesenchymal-epithelial transition (MET), including the exon 14 skipping mutation. MET tyrosine kinase stimulates cell scattering, invasion, protection from apoptosis, and angiogenesis. A variety of cancers (eg, lung, gastric) are associated with dysregulation of MET, owing to MET amplifications and exon 14 skipping mutations. Capmatinib is indicated for metastatic NSCLC in adults whose tumors have a mutation that leads to exon 14 skipping.

## Tepotinib (Tepmetko)

Tepotinib is an inhibitor of MET tyrosine kinase, which selectively binds to MET tyrosine kinase and disrupts MET signal transduction pathways. Therefore, this disruption may induce apoptosis in tumor cells overexpressing this kinase. It is indicated for metastatic NSCLC in patients with MET exon 14 skipping mutation.

## Trametinib (Mekinist)

Trametinib is a selective reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity. Trametinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity BRAF V600E mutations result in constitutive activation of the BRAF pathway, which includes MEK1 and MEK2. Trametinib inhibits cell growth in *BRAF* V600 mutation positive tumors in vitro and in vivo. It is indicated, in combination with dabrafenib, for the treatment of patients with metastatic NSCLC with *BRAF* V600E mutation as detected by an FDA-approved test.

## Telisotuzumab vedotin (Emrelis, Telisotuzumab vedotin-tllv)

Indicated for treatment of locally advanced or metastatic, non-squamous NSCLC harboring high c-MET protein overexpression (≥50% of tumor cells with strong [3+] staining) in adults who have received 1 prior systemic therapy

## **Antineoplastics, KRAS Inhibitors**

## 

*KRAS G12C* proteins continuously regenerate, so continuous inhibition is needed to prevent downstream signaling. Sotorasib and adagrasib form an irreversible, covalent bond with the unique cysteine of *KRAS G12C*, locking the protein in an inactive state that prevents downstream signaling without affecting wild-type K*RAS*. These inhibitors block KRAS signaling, inhibit cell growth, and promote apoptosis only in *KRAS G12C* tumor cell lines.

## Adagrasib (Krazati)

Indicated for *KRAS* G12C-mutated locally advanced or metastatic NSCLC in adults who have received 1 or more prior systemic therapies.

## Sotorasib (Lumakras)

Indicated for KRAS G12C-mutated locally advanced or metastatic NSCLC in adults who have received 1 or more prior systemic therapies.

## Antineoplastics, Monoclonal Antibodies

## Bevacizumab (Alymsys, Avastin, Avzivi)

Bevacizumab is a murine-derived monoclonal antibody that inhibits angiogenesis by targeting and inhibiting vascular endothelial growth factor (VEGF). It inhibits new blood vessel formation, denying blood, oxygen, and other nutrients needed for tumor growth. It is indicated in combination with carboplatin and paclitaxel for the first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic nonsquamous NSCLC. Mvasi has been FDA-approved as a biosimilar to Avastin but not as an interchangeable product.

## Ramucirumab (Cyramza)

Ramucirumab is a vascular endothelial growth factor receptor 2 (VEGFR2) antagonist that specifically binds VEGF receptor 2 and blocks binding of VEGFR ligands, VEGF-A, VEGF-C, and VEGF-D. As a result, it inhibits ligand-stimulated activation of VEGF2, thereby inhibiting ligand-induced proliferation, and migration of human endothelial cells. It is indicated in combination with erlotinib for first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

## **Antiemetic Agents**

## 

Antiemetic agents are useful in the treatment of symptomatic nausea caused by chemotherapy.

## Ondansetron (Zofran (DSC), Zofran ODT (DSC), Zuplenz (DSC))

Ondansetron blocks serotonin 5-HT3 receptor antagonists. It is not clear whether the effect is mediated centrally, peripherally, or both. Ondansetron is indicated in the prevention of chemotherapy-induced nausea and vomiting.

## Granisetron (Granisol Oral Solution, Sancuso, Sustol)

Granisetron blocks serotonin 5-HT3 receptor antagonists. It is not clear whether the effect is mediated centrally, peripherally, or both. Granisetron is indicated in the prevention of chemotherapy-induced nausea and vomiting.

## Dolasetron (Anzemet)

Dolasetron blocks serotonin 5-HT3 receptor antagonists. It is not clear whether the effect is mediated centrally, peripherally, or both. Dolasetron is indicated in the prevention of chemotherapy-induced nausea and vomiting.

## Palonosetron (Aloxi, Posfrea)

Palonosetron is a selective 5-HT3 receptor antagonist with a long half-life (40 h). It is indicated for the **p**revention of acute and delayed nausea and vomiting associated with initial and repeat courses of chemotherapy. It blocks 5-HT3 receptors peripherally and centrally in the chemoreceptor trigger zone.

## Dexamethasone (Baycadron, Decadron DSC, Dexamethasone Intensol)

Dexamethasone is a synthetic adrenocortical steroid with multiple indications. It is widely used in prevention of nausea and vomiting caused by highly emetogenic agents (eg, cisplatin) in combination with serotonin receptor antagonists.

## 

## **Doctor-Patient Conversation: Non-Small Cell Lung Cancer (NSCLC)**

Doctor: Thank you for coming in today. I have your test results, and I’d like to talk through them with you. The diagnosis is non-small cell lung cancer, or NSCLC, which is the most common type of lung cancer.

Patient: What does that mean for me? Where exactly is the cancer, and has it spread?

Doctor: NSCLC means the cancer started in your lungs, and it’s not the small cell type. Based on your scans, the cancer is located in [specific area], and right now, there is [no evidence/ some evidence] that it has spread to [lymph nodes/other organs]. We’ll use this information to determine the stage of your cancer, which helps guide our treatment choices.

Patient: What stage is my cancer, and what does that mean?

Doctor: The stage tells us how advanced the cancer is. For example, stage I means it’s small and only in the lung, while stage IV means it has spread to other parts of the body. Your cancer is stage [X], which means [brief explanation]. This information helps us decide on the best treatment plan for you.

Patient: What are my treatment options?

Doctor: Treatment depends on the stage, your overall health, and specific features of your cancer. Options may include surgery, radiation, chemotherapy, targeted therapy, or immunotherapy. We may also recommend biomarker testing to see if your cancer has certain gene changes that could help us choose the most effective treatment for you.

Patient: What are the side effects of treatment, and how will it affect my daily life?

Doctor: Each treatment has its own side effects. Surgery can involve recovery time, chemotherapy and radiation may cause fatigue, nausea, or hair loss, and targeted or immunotherapy can have other effects. We’ll go over the pros and cons of each option, and I’ll support you in managing any side effects so you can maintain your quality of life as much as possible.

Patient: How will we know if the treatment is working?

Doctor: We’ll monitor your progress with regular scans and blood tests. We’ll also check in about how you’re feeling and any symptoms you’re experiencing. If the treatment isn’t working as expected, we’ll discuss other options.

Patient: Are there clinical trials I should consider?

Doctor: There may be clinical trials available, depending on your specific situation. I can help you explore whether you’re eligible and what might be involved.

Patient: Is there anything I should do to get ready for treatment?

Doctor: It’s helpful to have support from family or friends, and to let us know about any other health issues you have. We’ll also talk about nutrition, exercise, and ways to manage stress during treatment.

Patient: Thank you for explaining everything.

Doctor: You’re welcome. Please write down any questions you have, and bring them to our next visit. We’re here to support you every step of the way.

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### 

### 

### **Small cell lung cancer**

Small cell lung cancer is a rare fast-growing lung cancer. Small cell lung cancer can affect anyone, but it typically affects people who have a long history of tobacco use, specifically smoking cigarettes. Healthcare providers can cure some people if the disease is found early; for others, they can help them live longer. The only way to prevent small cell lung cancer is to stop smoking.

#### **How common is this condition?**

Overall, about 57 in 100,000 people in the U.S. develop lung cancer. Small cell lung cancer represents about 15% of those cancer diagnoses. It’s less common than non-small cell lung cancer.

#### **How does small cell lung cancer affect my body?**

Small cell lung cancer starts when healthy cells in your lungs mutate or change into cancerous cells. These cells then divide and multiply uncontrollably. Eventually, the cancerous cells clump together in masses (tumors) in your lungs.

These tumors may shed cancer cells that your blood or lymph pick up and carry throughout your body. (Lymph is fluid that travels through your body to your lymph nodes.)

Small cell lung cancer typically spreads to:

* Lymph nodes.
* Bones.
* Brain.
* Liver.
* Adrenal glands. These glands are located near your kidneys.

Once the cells have spread, they may create new cancerous tumors in your lymph nodes and organs. Small cell lung cancer may also cause fluid to build up in your lungs or in the space around your lungs. It can make your lung collapse by pushing air out of your lung. This is called a pleural effusion.

##### **There are two types of small cell lung cancer:**

* Small cell carcinoma: This is the most common form of small cell lung cancer.
* Combined small cell carcinoma: Combined small cell carcinoma represents about 2% to 5% of all small cell carcinomas. This small cell type is a combination of non-small cell and small cell lung cancer cells.

## **Symptoms and Causes**

Small cell lung cancer that hasn’t spread rarely causes symptoms. When symptoms happen, they may include:

* Chest pain or discomfort.
* Chronic cough that doesn’t go away or worsens.
* Coughing up blood (hemoptysis).
* Difficulty breathing.
* Facial swelling.
* Fatigue.
* Hoarseness.
* Loss of appetite.
* Swollen neck veins.
* Unexplained weight loss.
* Wheezing.

Many of these symptoms are similar to other less serious conditions. Having one or more of these symptoms isn’t a sign you have small cell lung cancer. That said, if you smoke or you used to smoke and you notice these types of symptoms, talk to a healthcare provider. They’ll evaluate your situation and recommend any next steps.

### **What causes small cell lung cancer?**

While anyone can get lung cancer, people who smoke, used to smoke or who are exposed to tobacco smoke (second-hand smoke) have an increased risk of developing small cell lung cancer. Other risk factors include:

* Exposure to radiation from cancer treatments or imaging scans.
* Exposure to radon gas. Radon is a colorless radioactive gas that may seep into homes and other buildings.
* Exposure to workplace hazards like asbestos, arsenic, nickel, tar or toxic chemicals.
* Having a family history of lung cancer.
* Having human immunodeficiency virus (HIV).

## **Diagnosis and Tests**

Chest X-rays are typically the first step to evaluate someone for any type of lung cancer. If images show suspicious spots on your lung, a healthcare provider may order one or more of these diagnostic tests:

* Imaging scans: Computed tomography (CT) and positron emission tomography (PET) scans detect lung tumors. CT scans are the primary way to diagnose lung cancer. These tests also can help gauge cancer spread.
* Biopsy: A needle biopsy removes tissue samples from your lungs. Lab pathologists check the biopsy for cancer cells.
* Bronchoscopy: Using a bronchoscope, your provider looks inside of your lung’s airways for tumors. At the same time, they may remove tissue samples to biopsy.

#### **What are the stages of small cell lung cancer?**

Healthcare providers use a two-stage system to diagnose the spread of small cell lung cancer. This information also helps guide treatment. The two stages of small cell lung cancer are:

* Limited stage: This means there’s cancer in one of your lungs that may have spread to an area between your lungs or to lymph nodes just above your collarbone. About 1 out of 3 people with small cell lung cancer have limited stage cancer at diagnosis.
* Extensive stage: In extensive stage, the cancer has spread to your other lung or beyond your lungs to lymph nodes. It also may have spread to your bones, brain and other organs.

## **Management and Treatment**

Treatment depends on many factors including your age, overall health and cancer stage. Treatment options include:

* Surgery: About 1 in 20 people with small cell lung cancer have tumors that haven’t spread beyond their lung. In this circumstance, a surgeon may remove part of your lung or your entire lung. People who can’t have surgery may receive radiation therapy or chemotherapy.
* Radiation therapy: External radiation therapy uses a machine to deliver strong X-ray beams directly to the tumor. In addition to killing cancer cells, this therapy can relieve symptoms. Healthcare providers typically use radiation therapy to treat limited stage small cell lung cancer.
* Chemotherapy: If you had surgery, your healthcare provider may combine chemotherapy drugs with other treatments to kill lingering cancer cells. People with extensive stage cancer often receive chemotherapy. Chemotherapy can’t cure small cell lung cancer, but it can shrink cancer tumors, ease symptoms and help people to live longer.
* Immunotherapy: This treatment engages your body’s immune system to fight and destroy cancer cells. Immune checkpoint inhibitors are a type of immunotherapy that treats extensive small cell lung cancer. Healthcare providers may use this treatment along with chemotherapy to shrink cancer tumors and ease symptoms.

#### **What happens if I can’t have surgery and other treatments aren’t making a difference?**

There are options your healthcare provider may recommend and you may want to consider, such as:

* Shifting treatment from trying to cure small cell lung cancer to treatment that eases symptoms. For example, if your lung passages are blocked, your healthcare provider may use a bronchoscope to open those passages.
* Considering participating in a clinical trial. For example, recent clinical trials that combined chemotherapy and immunotherapy helped people with advanced small cell lung cancer to live longer. About 15% of people who received the combined treatment were alive three years after completing treatment.
* Considering palliative care: This care focuses on helping you manage symptoms, including pain, and cancer treatment side effects.

## **Outlook / Prognosis**

Small cell lung cancer is a very aggressive illness. Without treatment, most people with small cell lung cancer die a few months after they’re diagnosed. Healthcare providers can treat small cell lung cancer, but the disease often comes back. A 2020 study showed more than 50% of people treated for small cell lung cancer had a recurrence, meaning the cancer came back. According to 2020 data, about 7% of all people with small cell lung cancer were alive five years after diagnosis.

Many factors affect small cell lung cancer prognoses:

* The cancer stage: Healthcare providers have more success treating small cell lung cancer that hasn’t spread from where it started.
* Treatment options: Surgery to remove tumor is an option for 1 in 20 people with limited stage small cell lung cancer. People who can’t have surgery may receive chemotherapy and radiation therapy.
* Recurrence: Healthcare providers have fewer options for treating small cell lung cancer that comes back.

There’s no question that the prognoses for small cell lung cancer are grim. It’s important to remember a prognosis is what may happen, not what will happen. If you have small cell lung cancer and want to know your prognosis, ask your healthcare provider to explain what you may expect.

##### **What is the survival rate?**

Survival rates are estimates based on the experiences of groups of people. About 70% of people with small cell lung cancer aren’t diagnosed until after the cancer has spread (extensive-stage small cell lung cancer.) These people have fewer treatment options. According to 2020 data:

* Overall, 7% of all people with small cell lung cancer were alive five years after their diagnosis.
* About 27% of people with limited stage small cell lung cancer were alive five years after diagnosis. Someone with limited stage small cell lung cancer has cancer in one lung and nearby lymph nodes.
* About 16% of people with cancer that’s spread outside their lungs to nearby tissues and organs were alive five years after diagnosis.

Remember — just like prognoses, survival rates are estimates based on the experiences of groups of people. What’s happened to other people may not apply in your situation.

## **Prevention**

Avoiding tobacco is the best way to prevent small cell lung cancer. If you currently smoke tobacco, try to quit as soon as possible. Regardless of how old you are or how long you’ve been smoking, your lungs begin to heal as soon as you stop. Giving your lungs a chance to heal reduces your risk of developing small cell lung cancer. If you smoke tobacco and want to quit, ask a healthcare provider about smoking cessation treatment and programs.

#### **What about lung cancer screening tests?**

Unlike other types of lung cancer, there isn’t a screening test for small cell lung cancer.

#### **What else can I do to reduce my risk?**

These steps may also help:

* Maintain a weight that’s healthy for you.
* Eat a nutritious diet.
* Exercise regularly.
* Test your home for radon.
* Install a mitigation system to remove radon from your home, if needed.
* Protect yourself from cancer-causing chemicals (arsenic, asbestos, nickel) at work.

## **Living With**

Surgery and other cancer treatment can be physically challenging. You may feel exhausted after completing treatment. Here are some things you can do to stay strong through treatment:

* Eat a nutritious diet: The combination of cancer symptoms and cancer treatment can affect your appetite. If you’re having trouble eating, ask if you can work with a nutritionist. They’ll have suggestions for ways to make sure you’re getting the nutrition you need.
* Get some exercise: Cancer is stressful. Gentle exercise may help relieve stress.
* Seek support: Small cell lung cancer is a rare, incurable illness. It can be lonely to be one of the few people with a medical issue. Talk to a healthcare provider about support groups where you can connect with people who understand what you’re going through.
* Consider mental health support: You may feel you have to keep your cancer worries to yourself to avoid upsetting your loved ones. If that’s your situation, consider working with a mental health specialist.

### **What questions should I ask my healthcare provider?**

If you have small cell lung cancer, you may want to ask your healthcare provider:

## Why did I get small cell lung cancer?

## **Small cell lung cancer (SCLC) is most strongly linked to smoking tobacco—about 98% of all cases are in people with a history of smoking. Even secondhand smoke, exposure to radon, asbestos, uranium, and certain workplace chemicals can increase your risk. While anyone can develop SCLC, it is very rare in people who have never smoked. Family history and previous radiation exposure are additional, though less common, risk factors.**

## What stage is the lung cancer?

## **The stage of SCLC is determined by how far the cancer has spread. SCLC is often classified as:**

## **Limited stage: Cancer is confined to one lung and possibly nearby lymph nodes.**

## **Extensive stage: Cancer has spread to the other lung, distant lymph nodes, or other organs. Most people are diagnosed at the extensive stage because SCLC grows and spreads rapidly.**

## What does this mean for my prognosis?

## **SCLC is aggressive and often diagnosed after it has spread. Prognosis depends on the stage at diagnosis, your overall health, and how well the cancer responds to treatment. Limited stage SCLC has a better outlook than extensive stage, but overall, SCLC has a lower survival rate compared to other lung cancers due to its rapid progression.**

## What’s the best treatment for someone in my situation?

## **Treatment depends on the stage and your health:**

## **Limited stage: Often treated with chemotherapy and radiation therapy together.**

## **Extensive stage: Usually treated with chemotherapy, sometimes combined with immunotherapy and/or radiation to specific areas. Surgery is rarely used because SCLC is almost always widespread at diagnosis.**

## What are the treatment risks and side effects?

## **Chemotherapy: Fatigue, nausea, hair loss, lowered immunity, and increased risk of infection.**

## **Radiation therapy: Fatigue, skin changes, and possible effects on nearby organs.**

## **Immunotherapy: Can cause immune-related side effects like rash, diarrhea, or inflammation in organs. Your care team will discuss specific risks and help manage side effects.**

## Should I consider a clinical trial?

## **Yes, clinical trials may offer access to new treatments and are especially important for SCLC, which is challenging to treat. Ask your doctor about trials for which you may be eligible.**

## What type of follow-up care do I need after treatment?

## **Follow-up includes regular check-ups, imaging (like CT scans), and blood tests to monitor for recurrence or side effects. Your team will also watch for late side effects of treatment and help manage symptoms.**

## Will the cancer come back?

## **SCLC has a high risk of recurrence, even after successful initial treatment. The risk is higher for extensive stage disease. Ongoing monitoring is essential for early detection of recurrence.**

## What are the symptoms of recurring small cell lung cancer?

## **Symptoms may include:**

## **Persistent cough or shortness of breath**

## **Chest pain**

## **Unexplained weight loss**

## **Bone pain**

## **New neurological symptoms (headaches, weakness, confusion) If you notice any new or worsening symptoms, contact your doctor promptly.**

## How can I stop smoking?

## **Quitting smoking is the most important step you can take for your health. Resources include:**

## **Counseling and support groups**

## **Medications (nicotine replacement, prescription drugs)**

## **Additional Common Questions**

### **What is the difference between non-small cell lung cancer and small cell lung cancer?**

There are several differences:

* Small cell lung cancer typically starts in one kind of cell based in one area of your lung. Non-small cell cancer may start in three different kinds of cells and different areas of your body. For example, adenocarcinoma affects glands that line your organs. In non-small cell lung cancer, adenocarcinoma starts in the outer portions of your lungs.
* Small cell lung cancer spreads more quickly than non-small cell lung cancer.
* Viewed under a microscope, small cell lung cancer cells are much smaller than non-small cell lung cancer cells.

## **Differential Diagnoses**

### Atypical Carcinoid Lung Tumor

### Large Cell Neuroendocrine Carcinoma

### Lung Adenoma

### Lung Hamartoma Imaging

### Mediastinal Lymphoma

### Non-Small Cell Lung Cancer (NSCLC)

## 

## **Epidemiology**

### Occurrence in the United States

### Lung cancer overall is the second most common malignancy in both sexes in the United States, exceeded in frequency only by prostate cancer in men and breast cancer in women. In both sexes, lung cancer is the most common cause of cancer death. Although less than half as many new cases of lung cancer than breast cancer are diagnosed in US women each year, almost twice as many US women die of lung cancer each year than from breast cancer.

### The incidence of small cell lung cancer (SCLC) has declined over the last few years, as smoking rates have fallen.SCLC once accounted for 20-25% of all newly diagnosed lung cancers; it now comprises only about 13% of all lung cancers.

### For 2024, the estimates for lung cancer overall in the United States are 234,580 new cases and 125,070 deaths.

### International occurrence

### Globally, lung cancer is the most frequent malignancy in men (in Europe, lung cancer is second only to prostate cancer) and the fifth most common cancer in women. Although the incidence of lung cancer has been falling in the US, it is increasing at a staggering pace in developing countries due to the rising prevalence of tobacco use. According to World Health Organization (WHO) statistics, about 2.21 million new cases of lung cancer and 1.80 million deaths from lung cancer occurred worldwide in 2020.

### Separate worldwide data for SCLC are not available. The incidence of lung cancer started to decline among men in the early 1980s and has continued to do so over the past 20 years. In contrast, the incidence in women started to increase in the late 1970s and did not begin to decline until the mid-2000s.

### Age- and sex-related demographics

### As with other histopathologic types of lung cancer, most cases of SCLC occur in individuals aged 60-80 years.

### Over the past two decades, the incidence of lung cancer has generally decreased in both men and women 30 to 54 years of age in all races and ethnic groups. However, the incidence has declined more steeply in men. As a result, lung cancer rates in younger women have become higher than those in younger men. In non-Hispanic whites and Hispanics ages 44 to 49 years, for example, the female-to-male rate ratio for lung cancer incidence rose from 0.88 during 1995-1999 to 1.17 during 2010-2014.

### This reversal can be explained in part by increased rates of cigarette smoking in women born since 1965. However, while the difference in smoking rates in that age group has narrowed, rates in women have generally not exceeded the rates in men, so other factors may be playing a role. For example, women may be more susceptible to the oncogenic effects of smoking.

### **VALSG staging system**

### The Veterans Administration Lung Group (VALSG) staged small cell lung cancer (SCLC) into limited- and extensive-stage disease to distinguish between patients who may benefit from more aggressive, potentially curative treatments, such as chemotherapy combined with radiation therapy (limited-stage SCLC), and those individuals whose cancer is not likely to be cured with such therapy (extensive-stage SCLC).

### Limited-stage disease is confined not only to the ipsilateral hemithorax but also to an area that is small enough to be treated with radiation therapy in 1 tolerably safe radiation treatment port.

### **AJCC staging system**

### Under the new tumor, node, metastasis (TNM) staging system, from the American Joint Committee on Cancer (AJCC) (see tables 2 and 3, below), limited-stage SCLC is defined as any T, any N, M0; the exception is T3-4, owing to multiple lung nodules that extend beyond a single radiation field.

### Extensive-stage disease describes tumors that extend beyond the ipsilateral hemithorax, such as those that reach the contralateral lung and/or contralateral lymph nodes or that find their way to distant organs (eg, bone marrow).Approximately two thirds of patients with SCLC present with extensive-stage disease at diagnosis.The new TNM staging system classifies extensive-stage disease as any T, any N, M1a/b, and T3-4, due to involvement of multiple lung nodules.

### Table 2, below, summarizes the AJCC lung cancer TNM staging system categories, and Table 3, below, summarizes the lung cancer stage groupings.The TNM assignments define the cancer growth and disease extent, and the stage groupings combine cancers with a similar prognosis.Generally, lower stage numbers result in a better prognosis.

### Table 2. AJCC TNM Categories for Lung Cancer

| Primary Tumor (T) | | Tumor Size | Location of Involvement |
| --- | --- | --- | --- |
| TX | | Primary tumor can’t be assessed, or sputum cytology reveals tumor cells but the tumor is not seen on radiologic or bronchoscopic evaluation | |
| T0 | | No evidence of a primary tumor | |
| Tis | | Carcinoma in situ | |
| T1 | | ≤3 cm in greatest dimension | Surrounded by lung or visceral pleura; no invasion more proximal than lobar bronchus |
|  | T1a | ≤1 cm in greatest dimension |  |
|  | T1b | >1 cm but ≤2 cm in greatest dimension |  |
|  | T1c | >2 cm but ≤3 cm in greatest dimension |  |
| T2 | | >3 cm but ≤5 cm in greatest dimension, or(see right column) | Main bronchus, ≥2 cm distal to carina, orVisceral pleura, orHilar region, but not entire lung, associated with atelectasis/obstructive pneumonitis |
|  | T2a | >3 cm but ≤4 cm in greatest dimension |  |
|  | T2b | >5 cm but ≤7 cm in greatest dimension |  |
| T3 | | >5 cm but ≤7 cm in greatest dimension, or(see right column) | Direct invasion of:Parietal pleural chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, orMain bronchus < 2 cm distal to carina (but not carina itself), orEntire lung with associated atelectasis/obstructive pneumonitis, orSame lobe, separate tumor nodule(s) |
| T4 | | >7 cm or(see right column) | Invasion of:Mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carinaDifferent ipsilateral lobe, separate tumor nodule(s) |
| Node (N) | | Location of Regional Metastatic Involvement | |
| NX | | Regional lymph nodes cannot be assessed | |
| N0 | | No regional lymph node metastasis | |
| N1 | | Ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, andIntrapulmonary nodes, including direct extension | |
| N2 | | Ipsilateral mediastinal and/or subcarinal lymph node(s) | |
| N3 | | Contralateral mediastinal, contralateral hilar, ipsilateral/contralateral scalene, or supraclavicular lymph node(s) | |
| Metastasis (M) | | Location of Distant Metastatic Involvement | |
| M0 | | No distant metastasis | |
| M1 | | Distant metastasis | |
|  | M1a | Contralateral lobe tumor with separate tumor nodule(s), orTumor with pleural nodules or malignant pleural or pericardial effusion | |
|  | M1b | Single extrathoracic metastasis in a single organ and involvement of a single distant (non regional) node | |
|  | M1c | Multiple extrathoracic metastases in one or more organs | |
|  | | | |

### Table 3. AJCC Stage Groupings for Lung Cancer

|  | | Primary Tumor (T) | Regional Node (N) | Metastasis (M) |
| --- | --- | --- | --- | --- |
| Occult Cancer | | TX | N0 | M0 |
| Stage 0 | | Tis | N0 | M0 |
| Stage IA | IA1 | T1a | N0 | M0 |
| IA2 | T1b | N0 | M0 |
| IA3 | T1c | N0 | M0 |
| Stage IIA | | T2b | N0 | M0 |
| Stage IIB | | T1a,b,c | N1 | M0 |
| T2a,b | N1 | M0 |
| T3 | N0 | M0 |
| Stage IIIA | | T1a,b,c | N2 | M0 |
| T2a,b | N2 | M0 |
| T3 | N1-2 | M0 |
| T4 | N0-1 | M0 |
| Stage IIIB | | T1a,b,c | N3 | M0 |
| T2a,b | N3 | M0 |
| T3 | N2 | M0 |
| T4 | N2 | M0 |
| Stage IIIC | | T3-4 | N3 | M0 |
| Stage IVA | | Any T | Any N | M1a,b |
| Stage IVB | | Any T | Any N | M1c |

## 

## **Genomic Data of Small Cell Lung Cancer (SCLC)**

### Key Genomic Alterations:

### TP53 and RB1: Nearly all SCLC tumors have inactivating mutations in the tumor suppressor genes *TP53* and *RB1*. These mutations are considered foundational events in SCLC development and are present in the common ancestor clone of the tumor.

### MYC Family Amplifications: Amplifications in *MYC* family genes (such as *MYC*, *MYCL*, *MYCN*) are frequent but often not present in the founder clone. They are associated with tumor progression and may influence therapy response.

### Other Frequently Mutated Genes:

### *CREBBP* and *EP300*: Mutations in these chromatin-modifying genes are common and can be associated with genome duplications and resistance to therapy.

### *UNC13A*: Mutations in this gene have been linked to improved prognosis and better immune infiltration.

### *c-MET*: Mutations found in a small subset (about 4%) of SCLC cases, mainly among smokers, but have not shown a significant impact on survival.

### *EGFR*: Rare (about 2%), more likely in non-smokers and women, possibly associated with better outcomes.

## **Doctor-Patient Conversation: Small Cell Lung Cancer (SCLC)**

### 

### Doctor: Thank you for coming in today. I have your test results, and I’d like to talk through them with you. The diagnosis is small cell lung cancer, also known as SCLC.

### 

### Patient: What exactly does that mean?

### 

### Doctor: Small cell lung cancer is a type of lung cancer that tends to grow and spread quickly. It’s strongly linked to smoking, but it can happen to anyone. We found the cancer in your [lung/area], and we’re working to determine whether it’s limited to one area or has spread to other parts of your body. This helps us decide on the best treatment plan for you.

### 

### Patient: What stage is my cancer, and what does that mean for me?

### Doctor: SCLC is usually classified as either limited stage—meaning it’s confined to one lung and nearby lymph nodes—or extensive stage, where it has spread further. Most people are diagnosed at the extensive stage. This means our goal is to control the cancer, help you feel better, and hopefully help you live longer, but cure is less likely with extensive stage disease.

### Patient: What are my treatment options?

### Doctor: Treatment usually needs to start soon because SCLC can progress rapidly. For limited stage, we usually recommend chemotherapy and radiation together. For extensive stage, chemotherapy is the main treatment, sometimes combined with immunotherapy and radiation to certain areas. Surgery is rarely used for SCLC. We’ll also discuss whether you might benefit from brain radiation, as SCLC can sometimes spread to the brain.

### 

### Patient: What side effects should I expect?

### 

### Doctor: Chemotherapy can cause fatigue, nausea, hair loss, and increased risk of infection. Radiation may cause tiredness and skin changes. Immunotherapy, if used, can cause immune-related side effects. We’ll work closely with you to manage any side effects and help maintain your quality of life.

### 

### Patient: Should I consider a clinical trial?

### 

### Doctor: Yes, clinical trials may offer access to new treatments and are especially important for SCLC, which can be challenging to treat. We can look into trials that might be a good fit for you.

### 

### Patient: How urgent is it to start treatment, and will I have time to process everything?

### 

### Doctor: There is some urgency because SCLC can grow quickly, but it’s also important to take time to understand your options and ask questions. We’ll support you in making decisions that align with your goals and values.

### 

### Patient: What support is available for me and my family?

### 

### Doctor: You’ll have a team—including doctors, nurses, social workers, and patient navigators—to support you through treatment and beyond. Connecting with other patients and advocacy groups can also be very helpful.

### 

### Patient: Thank you for explaining everything.

### 

### Doctor: You’re welcome. Please write down any questions you have and bring them to our next visit. We’re here to support you every step of the way.

### REFERENCES

### [Small Cell Lung Cancer: Symptoms, Causes & Treatment](https://my.clevelandclinic.org/health/diseases/6202-small-cell-lung-cancer#overview)

<https://emedicine.medscape.com/article/280104-guidelines>

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### 

### **PANCREATIC CANCER**

**DEFINITION AND DESCRIPTION**

Pancreatic cancer occurs when cells in your pancreas mutate (change) and multiply out of control, forming a tumor. Your pancreas is a gland in your abdomen (belly), between your spine and stomach. It makes hormones that control blood-sugar levels and enzymes that aid in digestion.

Most pancreatic cancers start in the ducts of your pancreas. The main pancreatic duct (the duct of Wirsung) connects your pancreas to your common bile duct.

Early-stage pancreatic tumors don’t show up on imaging tests. For this reason, many people don’t receive a diagnosis until the cancer has spread (metastasis). Pancreatic cancer is also resistant to many common cancer drugs, making it notoriously difficult to treat.

Ongoing research focuses on early detection through genetic testing and new imaging methods. Still, there’s much to learn.

#### **Types of pancreatic cancer**

There are two main types of pancreatic tumors:

1. Exocrine tumors: Over 90% of all pancreatic tumors are exocrine tumors. The most common type of pancreatic cancer is adenocarcinoma, which begins in the cells that line your organs.
2. Neuroendocrine tumors: Less than 10% of pancreatic tumors are neuroendocrine tumors (NETs). Islet cell carcinoma is another name for an NET.

Pancreatic cancer is responsible for approximately 3% of all cancers in the United States. It’s the 10th most common cancer in men and the 8th most common cancer in women.

Cases of pancreatic cancer are on the rise. Trends indicate that pancreatic cancer will be the second leading cause of cancer death in the United States by 2030.

## **Symptoms and Causes**

Warning signs of pancreatic cancer and how to spot them.

### **Symptoms of pancreatic cancer**

Unfortunately, there aren’t any early signs of pancreatic cancer. Symptoms typically emerge once the tumor starts impacting other organs in your digestive system.

Pancreatic cancer symptoms may include:

* Jaundice (yellowing of your skin).
* Dark urine (pee).
* Light-colored stool (poop).
* Upper abdominal pain.
* Middle back pain.
* Fatigue.
* Itchy skin.
* Nausea and vomiting.
* Gas or bloating.
* Lack of appetite.
* Blood clots.
* Weight loss.
* New-onset diabetes.

Your healthcare provider might suspect pancreatic cancer if you’ve recently developed diabetes or pancreatitis — a painful condition due to inflammation in your pancreas.

Symptoms of pancreatic neuroendocrine cancer may be different from traditional pancreatic cancer symptoms, such as jaundice or weight loss. Symptoms can vary, but may include diarrhea and anemia.

#### **How long does it take to notice pancreatic cancer?**

There are no tell-tale early signs of pancreatic cancer. Some people develop vague symptoms up to one year before they receive a diagnosis.

Many people report that their first pancreatic cancer symptoms were back pain or stomach pain. These symptoms can come and go at first, but may get worse after meals or when you lie down.

### **What causes pancreatic cancer?**

There isn’t a clear answer. We don’t know exactly what causes pancreatic cancer. But experts have identified some risk factors.

#### **Pancreatic cancer risk factors**

A risk factor is something that increases your chances of getting a certain disease. Common pancreatic cancer risk factors include:

* Smoking cigarettes, cigars and using other forms of tobacco.
* Obesity, particularly if you carry extra weight around your waist.
* Diabetes, especially Type 2 diabetes. Sudden-onset diabetes could be a sign of pancreatic cancer.
* Exposure to certain chemicals, like pesticides and petrochemicals.
* Chronic pancreatitis, a permanent inflammation of your pancreas.
* Hereditary chronic pancreatitis due to gene changes (mutations) passed from biological parent to child.
* Hereditary syndromes with changes (mutations) in genes, such as *BRCA1* or *BRCA2* genes passed from biological parent to child.

### **Complications of pancreatic cancer**

Pancreatic cancer tends to spread (metastasize) to nearby blood vessels, lymph nodes, and then to your liver, peritoneum (the lining of your abdominal cavity) and lungs.

The majority of pancreatic cancers have already spread beyond the pancreas at the time of diagnosis.

## **Diagnosis and Tests**

It’s difficult to detect pancreatic cancer in the early stages. This is because healthcare providers can’t feel your pancreas during routine exams and it’s difficult to see these tumors on routine imaging tests.

If your provider suspects pancreatic cancer, they’ll recommend a combination of pancreas function tests, which may include:

#### **Imaging tests**

Your healthcare provider may need to take one or more of the following imaging tests:

* CT (computed tomography) scans.
* MRI (magnetic resonance imaging).
* PET (positron emission tomography).
* Endoscopic ultrasound (EUS).

#### **Blood tests**

A pancreas blood test can detect tumor markers. A tumor marker is a substance that may indicate the presence of cancer.

For pancreatic cancer, high levels of carbohydrate antigen (CA) 19-9 — a type of protein released by pancreatic cancer cells — might indicate a tumor.

#### **Staging laparoscopy**

Sometimes, providers use laparoscopy to determine the extent of pancreatic cancer and whether removal is possible.

During this procedure, a surgeon creates a few small incisions (cuts) in your abdomen and inserts a long tube with a camera on the end. This allows them to see inside your abdomen and look for abnormalities. Often, they’ll take a biopsy during the same procedure.

#### **Genetic testing**

If you receive a pancreatic cancer diagnosis, you should consider genetic testing. This can tell you if there’s a hereditary reason you developed pancreatic cancer. It can also help your healthcare provider determine which type of treatment will be most effective for you.

Some people with pancreatic cancer have mutations in genes *BRCA1* and *BRCA2*. Though you may recognize these genes as the “breast cancer genes,” mutations in *BRCA1* and *BRCA2* may also indicate other types of cancer, including prostate, ovarian and pancreatic.

If you’re a first-degree relative (a parent, child or sibling) of someone who has pancreatic cancer, you should consider genetic testing. Your results can tell you if you have a *BRCA1* or *BRCA2* gene mutation. Keep in mind, even if you have the mutation, it doesn’t mean you’ll get cancer. But knowing your risk is important.

### **Resectable vs. unresectable pancreatic cancer**

Healthcare providers rank pancreatic tumors into four different categories:

* Resectable: The tumor is only in your pancreas and doesn’t involve nearby blood vessels or other organs. A provider can remove it with surgery.
* Borderline resectable: The tumor is in your pancreas and there’s some involvement of nearby blood vessels, but a surgeon can still remove it.
* Locally advanced: The tumor is in your pancreas and has significant involvement of nearby blood vessels. In these cases, surgical removal might be difficult or unsafe.
* Metastatic: The cancer has spread to distant areas in your body, such as your liver, lungs or abdominal cavity. It has possibly spread to organs, tissues or lymph nodes near your pancreas.

If you have specific questions about pancreatic cancer staging, talk to your healthcare provider. Understanding your pancreatic cancer diagnosis can help you make an informed decision about your treatment.

## **Management and Treatment**

Even though pancreatic cancer has a poor survival rate, complete remission is possible with early detection and treatment. The only way to realistically cure pancreatic cancer is total surgical removal of the cancer.

Specific treatment depends on certain factors, including:

* The exact location of the tumor.
* What stage it is.
* Your overall health.
* Whether the cancer has spread beyond your pancreas.

Pancreatic cancer treatments include:

#### **Surgery**

Surgery is the only realistic way to cure pancreatic cancer. But surgeons only recommend it when they think they can remove all of the cancer. Otherwise, there’s little to no benefit.

For surgery to be successful, the cancer must be completely confined to the pancreas. Even then, total cancer removal may not be possible.

There are a few different surgical techniques, depending on the location and size of the tumor:

##### **Whipple procedure (pancreaticoduodenectomy)**

If the tumor is in the head of your pancreas (the widest part of your pancreas, near your small intestine), your provider may recommend the Whipple procedure. This surgical approach removes the head of your pancreas, your duodenum (the first portion of your small intestine), your gallbladder, a portion of your bile duct and nearby lymph nodes.

Your surgeon will then attach your remaining bile duct and pancreas to your small intestine. This reestablishes your digestive tract.

##### **Distal pancreatectomy**

If the tumor is in the tail of your pancreas, a surgeon can perform a distal pancreatectomy. During this procedure, a surgeon removes the tail of your pancreas and some of the pancreas body. In most cases, they’ll also remove your spleen.

As your spleen helps fight infections, your healthcare provider may recommend getting certain vaccinations before having a distal pancreatectomy.

##### **Total pancreatectomy**

If cancer has spread throughout your entire pancreas, but resection (removal) is still possible, your healthcare provider may consider a total pancreatectomy. This surgery removes your entire pancreas, gallbladder, spleen and part of your stomach and small intestine.

It’s possible to live without a pancreas, but it can cause major side effects. Your pancreas makes insulin and other hormones that keep blood sugar at a safe level. Without a pancreas, you’ll develop diabetes and need insulin shots to survive. Additionally, you’ll need to take pancreatic enzyme pills to help with digestion.

#### **Chemotherapy**

Chemotherapy uses drugs that kill cancer cells. Healthcare providers give these drugs in pill form or through an IV in your arm.

Providers use chemotherapy as a stand-alone treatment — especially for people with advanced pancreatic cancer. They may also recommend chemotherapy before surgery to shrink the tumor or after surgery to kill any remaining cancer cells.

#### **Radiation therapy**

Radiation therapy uses high-energy X-rays to kill cancer cells. Healthcare providers commonly use this approach to treat pancreatic cancer.

Most often, providers combine radiation therapy with chemotherapy (chemoradiation). They may recommend it before surgery, after surgery or as part of your main cancer treatment. Radiation therapy can also help ease pancreatic cancer symptoms in people who don’t qualify for surgery (in cases of advanced cancer).

#### **Targeted therapy**

This treatment uses drugs that “target” certain proteins. These proteins control how cancer cells grow and spread. Providers may combine targeted therapy with other treatments like radiation therapy.

Common targeted therapy drugs for pancreatic cancer include:

* Erlotinib.
* Olaparib.
* Larotrectinib.
* Entrectinib.

#### **Pain management**

Pancreatic cancer could be very painful as it may involve nearby nerves. Your healthcare provider can help you manage pain with oral medications, anesthesia or steroid injections.

If you have pancreatic cancer and start to develop severe and persistent pain, tell your healthcare provider. They can find a treatment that will ease your symptoms.

## **Outlook / Prognosis**

A pancreatic cancer diagnosis can feel overwhelming. Because everyone is unique, no two cases are the same. Your healthcare provider will assemble a team of experts to determine the best treatment plan for your situation. Your medical team may include:

* Gastroenterologist.
* Pathologist.
* Oncologists (medical, surgical and radiation).
* Social worker.

#### **Pancreatic cancer progression timeline**

Generally, it takes about 10 to 20 years for a single cancer cell in your pancreas to turn into a tumor. The goal of ongoing research is to determine how healthcare providers can detect pancreatic cancer in its earliest stages, when it’s more treatable.

#### **Pancreatic cancer survival rate**

In the United States, the five-year survival rate for people with pancreatic cancer is 11%. This means that 11 out of 100 people are still alive five years after their diagnosis.

Survival rates are only estimates. They can’t tell you how long you’ll live or how well you’ll respond to treatment. If you have specific questions about survival rates and what they mean for you, talk to your healthcare provider.

## **Prevention**

You can’t prevent pancreatic cancer. But there are things you can do to lower your risk:

* Don’t smoke.
* Limit your alcohol intake.
* Eat lots of fresh fruit, vegetables and whole grains.
* Reduce your intake of red meat, sugary drinks and processed foods.
* Limit your exposure to harmful chemicals, such as asbestos, pesticides and petrochemicals.
* Maintain a weight that’s healthy for you.

#### **Pancreatic cancer screenings**

Healthcare providers don’t usually perform routine screenings for pancreatic cancer. But in people with a high risk of pancreatic cancer due to genetic predisposition, providers recommend monitoring with imaging tests and endoscopic ultrasounds.

If you have a first-degree family member (parents or siblings) with pancreatic cancer, you should talk to a healthcare provider about your risk of developing pancreatic cancer and proper screening and genetic tests.

## 

### **When should I see my healthcare provider?**

There are no clear-cut symptoms for early-stage pancreatic cancer. However, you should see a healthcare provider right away if you develop:

* Jaundice.
* Stomach or back pain.
* Unexplained weight loss.
* Sudden onset of diabetes.

## **Diagnostic Considerations**

### Pancreatic cancer is notoriously difficult to diagnose in its early stages. For example, the National Comprehensive Cancer Network (NCCN) recommends that clinicians consider pancreatic cancer in patients with diabetes who have unusual symptoms such as continuous weight loss and abdominal problems.

### Many patients have sought care for symptoms for weeks or months before receiving a definitive diagnosis of pancreatic cancer; in the past, fewer than a third of patients were diagnosed within 2 months of the onset of their symptoms. However, the availability of CT scanning has shortened that interval. Even so, at the time of diagnosis, 51% of all patients with pancreatic cancer have distant disease and 29% have regional spread.

### In addition to the differentials listed in the next section, diseases that can mimic the symptoms of pancreatic cancer include the following:

### Abdominal aortic aneurysm

### Ampullary carcinoma

### Intestinal ischemia

### Gastric lymphoma

### Pancreatic lymphoma

### Hepatocellular carcinoma (hepatoma)

### Bile duct strictures

### Bile duct tumors

### Neoplasms of the endocrine pancreas

## Differential Diagnoses

### Acute Pancreatitis

### Cholangitis

### Acute Cholecystitis

### Choledochal Cysts

### Chronic Pancreatitis

### Gallstones (Cholelithiasis)

### Gastric Cancer

### Peptic Ulcer Disease

## 

## **Epidemiology**

### Incidence in the United States

### The American Cancer Society estimates that in the United States in 2024, about 66,440 new cases of pancreatic cancer (34,530 in men and 31,910 in women) will be diagnosed.Over 2010-2019, age-adjusted rates for new pancreatic cancer cases rose on average 0.9% each year.

### International incidence

### Worldwide, pancreatic cancer ranks 11th in incidence but 7th as a cause of cancer death.The age-standardized rate (ASR) incidence ranges widely, from 7.7 per 100,000 population in Europe to 2.2 per 100,000 population in Africa. Among individual countries, ASRs range from 0.81 per 100,000 in males in India to 15.3 per 100,000 in males in Latvia and the Republic of Moldova.

### Race predilection

### From 2016 to 2020, the highest incidence rate of pancreatic cancer in the United States was 17.6 cases per 100,000 persons per year, in Black men. The incidences in men in other racial/ethnic groups were as follows:

### White: 15.1

### Hispanic: 12.7

### American Indian/Alaska Native: 16.5

### Asian/Pacific Islander: 10.9

### The incidences in US women during that period were as follows:

### Black: 14.9

### White: 11.8

### Hispanic: 11.3

### American Indian/Alaska Native: 11.0

### Asian/Pacific Islander: 9.2

### Age predilection

### In the absence of predisposing conditions, such as familial pancreatic cancer and chronic pancreatitis, pancreatic cancer is unusual in persons younger than 45 years. After age 50 years, the frequency of pancreatic cancer increases linearly. About 90% of patients are 55 years or older at diagnosis; the median age at diagnosis is 70 years.

### However, emerging data are showing a disproportionate increase in early-onset pancreatic cancer (ie, before age 50-55 years), especially in women.Risk factors such as obesity and smoking may be driving this trend.

### Mortality

### Although pancreatic cancer constitutes only about 3% of all cancers in the United States, it is the fourth leading cause of cancer deaths in both men and women, being responsible for 8% of all cancer-related deaths.The American Cancer Society estimates that in the United States in 2024, about 51,750 people (27,270 men and 24,480 women) will die of pancreatic cancer. During 2008 to 2017, the death rate for pancreatic cancer increased slightly (by 0.4% per year) in Whites and decreased slightly (by 0.5% per year) in Blacks.

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### **RECOMMENDATION**

### The consortium recommends screening for stage I pancreatic cancer and pancreatic cancer precursor lesions with high-grade dysplasia in the following high-risk groups:

### All patients with Peutz-Jeghers syndrome (carriers of a germline *LKB1/STK11* gene mutation)

### All carriers of a germline *CDKN2A* mutation

### Carriers of a germline *BRCA2, BRCA1, PALB2, ATM, MLH1, MSH2*, or *MSH6* gene mutation with at least one affected first-degree blood relative

### Individuals who have at least one first-degree relative with pancreatic cancer who in turn also has a first-degree relative with pancreatic cancer (familial pancreatic cancer kindred)

### The recommended age at which to start surveillance varied by gene mutation status and family history, as follows:

### Familial pancreatic cancer kindred (without a known germline mutation) - Start at age 50 or 55, or 10 years younger than the youngest affected blood relative

### *CDKN2A* or Peutz-Jegher syndrome - Start at age 40

### *BRCA2,ATM, PALB2 BRCA1, MLH1/MSH2 - S*tart at age 45 or 50, or 10 years younger than the youngest affected blood relative

### Recommended screening techniques are as follows:

### At baseline - Magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP) plus endoscopic ultrasound (EUS) plus fasting blood glucose and/or HbA1c

### During follow up - Alternate MRI/MRCP and EUS; routinely test fasting blood glucose and/or HbA1c

### As indicated - Serum CA 19–9, if concerning features on imaging; EUS-FNA only for solid lesions of ≥5 mm, cystic lesions with worrisome features, or asymptomatic main pancreatic duct (MPD) strictures (with or without mass); CT only for solid lesions, regardless of size, or asymptomatic MPD strictures of unknown etiology (without mass)

### The consortium recommends a screening interval of every 12 months in patients with no abnormalities, or only non-concerning abnormalities (eg, pancreatic cysts without worrisome features), and every 3 or 6 months in patients with abnormalities that are not suspicious for malignancy but are concerning; immediate surgical resection is indicated for abnormalities suspicious for malignancy.

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### *American Gastroenterological Association recommendations*

### In 2020, the AGA published a clinical practice guideline update containing best practice advice for identifying and screening patients at high risk for pancreatic cancer. The goal of screening is to detect resectable stage 1 pancreatic ductal adenocarcinoma, and high-risk precursor neoplasms such as intraductal papillary mucinous neoplasms (IPMNs) with high-grade dysplasia and some enlarged pancreatic intraepithelial neoplasias.

### The guideline recommends against screening average-risk individuals for pancreas cancer. The guideline recommends considering screening in patients determined to be at high risk, including first-degree relatives of patients with pancreas cancer with at least two affected genetically related relatives, and in patients with genetic syndromes associated with an increased risk of pancreas cancer, including all patients with the following:

### Peutz-Jeghers syndrome

### Hereditary pancreatitis

### *CDKN2A* gene mutation

### One or more first-degree relatives with pancreas cancer with Lynch syndrome

### Mutations in *BRCA1, BRCA2, PALB2*, and *ATM* genes

### Further recommendations are as follows:

### Consider genetic testing and counseling for familial pancreas cancer relatives who are eligible for surveillance. A positive germline mutation is associated with an increased risk of neoplastic progression and may also lead to screening for other relevant associated cancers.

### When possible, high-risk patients undergoing pancreas cancer screening should participate in a registry or be referred to a pancreas center of excellence.

### Begin pancreas cancer screening in high-risk individuals at age 50, or 10 years younger than the initial age of familial onset. Initiate screening at age 40 in *CKDN2A* and *PRSS1* mutation carriers with hereditary pancreatitis and at age 35 in patients with Peutz-Jeghers syndrome.

### MRI and EUS in combination are the preferred screening modalities for pancreas cancer screening.

### Screening intervals of 12 months should be considered when there are no concerning pancreas lesions, with shortened intervals and/or the performance of EUS in 6-12 months directed towards lesions determined to be low risk (by a multidisciplinary team). EUS evaluation within 3-6 months for indeterminate lesions and within 3 months for high-risk lesions, if surgical resection is not planned. New-onset diabetes in a high-risk patient should lead to additional diagnostic studies or change in surveillance interval.

### Decisions regarding therapy directed towards abnormal findings detected during screening should be made by a dedicated multi-disciplinary team together with the high risk individual and their family.

### Surgical resection should be performed at high volume centers.

### Consider discontinuing pancreas cancer screening in high-risk individuals when they are more likely to die of causes unrelated to pancreas cancer, due to co-morbidity and/or are not candidates for pancreas resection.

### The limitations and potential risks of pancreas cancer screening should be discussed with patients prior to initiating a screening program.

### **Use of Tumor Markers in Pancreatic Cancer**

### The recommendations for evaluation of CA 19-9 levels are as follows:

### CA 19-9 is least sensitive for small, early-stage pancreatic carcinomas and thus is not effective for the early detection of pancreatic cancer or as a screening tool

### Use of CA 19-9 levels alone is not recommended for use in determining operability

### Rising levels of CA 19-9 postoperatively may predict recurrent disease, but confirmation with imaging studies and/or biopsy is required.

### CA 19-9 can be measured at the start of treatment for locally advanced metastatic disease and every 1-3 months during active treatment; elevation of levels in serial determinations may be an indication of progressive disease, but confirmation with other studies is required

### 5-10% of patients lack the enzyme necessary to produce CA 19-9; in these patients with low or absent titer of CA 19-9, monitoring disease with this tumor marker will not be possible

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### Guidelines for diagnosis and treatment of pancreatic cancer recommend the measurement of serum CA 19-9 levels after surgery and before adjuvant therapy to guide treatment and follow up.

### Diabetes Mellitus as Risk Factor

### The NCCN guideline for pancreatic adenocarcinoma acknowledges long-standing diabetes mellitus as a risk factor for pancreatic cancer. The guideline also notes an association between sudden onset of type 2 diabetes mellitus in an adult older than 50 years and a new diagnosis of pancreatic cancer. NCCN guidelines state that clinicians should consider pancreatic cancer in patients with diabetes who have unusual symptoms such as continuous weight loss and abdominal problems.

### **TREATMENT DRUG INFORMATION**

## **Antineoplastic agents**

## 

These agents inhibit cell growth and proliferation. They are used for chemotherapy.

## Gemcitabine (Gemzar, Infugem)

A frequently quoted trial showed a small, but statistically significant, improvement in overall survival in pancreatic cancer patients with gemcitabine versus 5-FU (5.7 vs 4.4 mo). Additionally, gemcitabine improved the quality of life in approximately 25% of patients. It is a pyrimidine antimetabolite that inhibits DNA polymerase and ribonucleotide reductase, which in turn inhibits DNA synthesis.

## Fluorouracil (Adrucil)

This is a fluorinated pyrimidine antimetabolite that inhibits thymidylate synthase (TS) and also interferes with ribonucleic acid (RNA) synthesis and function. Fluorouracil has some effect on DNA and is useful in symptom palliation for patients with progressive disease. It is commonly used in patients with gastrointestinal malignancies. Response rates are typically less than 20% in pancreatic cancer.

## Capecitabine (Xeloda)

Capecitabine is a prodrug of fluorouracil that undergoes hydrolysis in liver and tissues to form the active moiety (fluorouracil), inhibiting thymidylate synthetase, which in turn blocks methylation of deoxyuridylic acid to thymidylic acid. This step interferes with DNA, and to a lesser degree with RNA synthesis.

## Erlotinib (Tarceva)

This agent is pharmacologically classified as a human epidermal growth factor receptor type 1/epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor. EGFR is expressed on the cell surface of normal cells and cancer cells. Erlotinib has been approved by the FDA for use, in combination with gemcitabine, as a first-line treatment for locally advanced, unresectable, or metastatic pancreatic cancer.

## Paclitaxel protein bound (Abraxane)

Paclitaxel protein bound is a microtubular inhibitor (albumin-conjugated formulation) and a natural taxane that prevents depolymerization of cellular microtubules, which results in DNA, RNA, and protein synthesis inhibition. It is indicated for metastatic adenocarcinoma of the pancreas as first-line treatment in combination with gemcitabine.

## Irinotecan liposomal (Onivyde)

Irinotecan sucrosofate salt in a pegylated liposomal formulation. Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase-1 DNA complex and prevent re-ligation of the single-strand breaks, leading to exposure time-dependent double-strand DNA damage and cell death. Irinotecan liposomal is used in combination with fluorouracil and leucovorin for metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. It also indicated in combination with oxaliplatin, fluorouracil, and leucovorin for first-line treatment of adults with metastatic pancreatic adenocarcinoma.

## Olaparib (Lynparza)

Olaparib is a poly (DP-ribose) polymerase (PARP) inhibitor. PARP enzymes are involved in normal cellular function (eg, DNA transcription and repair). It is indicated for maintenance treatment of adults with deleterious or suspected deleterious germline BRCA-mutated metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.

## Oxaliplatin (Eloxatin (DSC))

Platinum coordination compound that inhibits DNA synthesis; cross-links and denatures strands of DNA; disrupts DNA function by covalently binding to DNA bases.

## **Anti-NRG Monoclonal Antibodies**

## Zenocutuzumab (Zenocutuzumab-zbco, Bizengri)

Bispecific HER2-and HER3-directed antibody that reduces cell growth in neuregulin 1 (NRG1) fusion-positive tumors.

### **Common Questions**

What stage is the cancer?

What does this mean for me?  
The stage describes how far the cancer has spread. Early-stage (localized) cancers may be eligible for surgery, which offers the best chance for long-term survival. Locally advanced or metastatic cancers (spread beyond the pancreas) are usually treated with chemotherapy, radiation, or targeted therapies. Staging helps determine your treatment options and prognosis.

What are my treatment options?

Which do you recommend and why?  
Treatment depends on the stage and your overall health:

* Surgery: For early-stage, resectable tumors.
* Chemotherapy: Used before or after surgery, or as the main treatment if surgery isn’t possible.
* Radiation therapy: Sometimes combined with chemotherapy.
* Targeted therapy or immunotherapy: For select patients with specific genetic changes or in clinical trials.
* Palliative care: To manage symptoms and improve quality of life at any stage.  
  Your care team will recommend the best approach based on your cancer’s characteristics and your health.

What side effects might I develop as a result of treatment?

* Surgery: Pain, infection, digestive issues, and delayed recovery.
* Chemotherapy: Fatigue, nausea, hair loss, risk of infection, and appetite loss.
* Radiation: Fatigue, skin changes, and digestive symptoms.
* Targeted therapies: Side effects depend on the drug, but may include diarrhea, skin rash, or high blood pressure.  
  Your team will help manage side effects and support your recovery.

Is genetic testing right for me?  
Yes, genetic testing is often recommended. It can identify inherited mutations (which may affect your family) and tumor mutations (which may help guide targeted therapy or clinical trial options).

Are there clinical trials available?  
Yes, clinical trials are available for many stages of pancreatic cancer and may offer access to new treatments, including novel drugs, targeted therapies, and immunotherapies. Your doctor can help you find suitable trials.

Will I be able to keep working and doing the things that I need to do every day?  
Many people can continue daily activities, but treatment may cause fatigue or other side effects that require rest or adjustments to your routine. Your ability to work will depend on your treatment plan, side effects, and personal situation. Discuss your goals and needs with your care team for personalized advice.

Can you tell me where to find financial support?  
Cancer centers often have social workers or financial counselors who can help you navigate insurance, apply for assistance, and connect you with resources. National organizations like the Pancreatic Cancer Action Network (PanCAN) and the American Cancer Society also offer financial support and guidance.

Can you tell me where to find emotional support?  
Emotional support is available through hospital-based counseling, support groups, and national organizations. Many cancer centers offer access to psychologists, social workers, and peer support programs. Online and in-person support groups are also available through organizations like PanCAN and the Cancer Support Community.

What should I do to stay as healthy as I can?

* Eat a balanced diet and consider meeting with a nutritionist.
* Stay as active as possible, within your limits.
* Take medications as prescribed, including pancreatic enzyme supplements if needed.
* Attend all follow-up appointments.
* Seek support for emotional well-being.
* Avoid tobacco and limit alcohol use

### What are some signs that pancreatic cancer has spread?

As pancreatic cancer progresses, you may develop new symptoms. Advanced pancreatic cancer symptoms may include:

* Abdominal pain.
* Extreme fatigue.
* Unexplained weight loss.
* Jaundice.
* Fluid buildup and swelling in your abdomen (ascites).

## **Doctor-Patient Conversation: Pancreatic Cancer**

Doctor: Thank you for coming in today. I have the results of your tests, and I want to talk through them with you. The diagnosis is pancreatic cancer.

Patient: That’s a lot to take in. What does this mean for me?

Doctor: I understand this is difficult news. The next step is to determine the stage of your cancer—meaning how far it has spread. This helps us decide on the best treatment options and what to expect moving forward. Some pancreatic cancers can be removed with surgery, while others may need chemotherapy or other treatments first.

Patient: What are my treatment options?

Doctor: Treatment depends on the stage and your overall health. Options may include surgery, chemotherapy, radiation, or a combination. For some patients, targeted therapies or clinical trials may also be appropriate. We’ll discuss the pros and cons of each option and tailor the plan to your needs.

Patient: What side effects might I have from treatment?

Doctor: Side effects depend on the treatment. Surgery can cause pain and digestive changes. Chemotherapy may cause fatigue, nausea, or increased risk of infection. Radiation can cause tiredness and digestive symptoms. We’ll help you manage any side effects and support your recovery.

Patient: Should I have genetic testing?

Doctor: Genetic testing is often recommended for people with pancreatic cancer. It can help us find inherited mutations that might affect your treatment or your family’s risk. It may also reveal changes in the tumor that could guide targeted therapy or clinical trial options.

Patient: Are there clinical trials available for me?

Doctor: Yes, there are clinical trials for many stages of pancreatic cancer. These may offer access to new treatments. I can help you find out if you’re eligible for any trials.

Patient: Will I be able to keep working or doing my daily activities?

Doctor: Many people can continue some daily activities, but treatment may cause fatigue or other side effects. We’ll work together to support your quality of life and adjust your plan as needed.

Patient: Where can I find financial or emotional support?

Doctor: Our cancer center has social workers and financial counselors who can help with insurance and costs. We also have counselors and support groups for emotional support. National organizations like the Pancreatic Cancer Action Network provide resources as well.

Patient: What should I do to stay as healthy as I can?

Doctor: Eat a balanced diet, stay as active as possible, take medications as prescribed, and let us know about any new symptoms. Emotional well-being is also important, so please reach out if you need support.

Doctor: Please write down any questions you have and bring them to our next visit. We’re here to support you every step of the way.

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**GASTRIC(STOMACH) CANCER**

**DEFINITION AND DESCRIPTION**

Stomach cancer, which is also called gastric cancer, is a growth of cells that starts in the stomach. The stomach is in the upper middle part of the belly, just below the ribs. The stomach helps to break down and digest food.

Stomach cancer can happen in any part of the stomach. In most of the world, stomach cancers happen in the main part of the stomach. This part is called the stomach body.

In the United States, stomach cancer is more likely to start by the gastroesophageal junction. This is the part where the long tube that carries food you swallow meets the stomach. The tube that carries food to the stomach is called the esophagus.

Where the cancer starts in the stomach is one factor health care providers think about when making a treatment plan. Other factors might include the cancer's stage and the type of cells involved. Treatment often includes surgery to remove the stomach cancer. Other treatments may be used before and after surgery.

Stomach cancer treatment is most likely to be successful if the cancer is only in the stomach. The prognosis for people with small stomach cancers is quite good. Many can expect to be cured. Most stomach cancers are found when the disease is advanced and a cure is less likely. Stomach cancer that grows through the stomach wall or spreads to other parts of the body is harder to cure.

**Causes**

It's not clear what causes stomach cancer. Experts believe most stomach cancers start when something hurts the inside lining of the stomach. Examples include having an infection in the stomach, having long-standing acid reflux and eating a lot of salty foods. Not everyone with these risk factors gets stomach cancer, though. So more research is needed to find out exactly what causes it.

Stomach cancer begins when something hurts cells in the inner lining of the stomach. It causes the cells to develop changes in their DNA. A cell's DNA holds the instructions that tell a cell what to do. The changes tell the cells to multiply quickly. The cells can go on living when healthy cells would die as part of their natural lifecycle. This causes a lot of extra cells in the stomach. The cells can form a mass called a tumor.

Cancer cells in the stomach can invade and destroy healthy body tissue. They might start to grow deeper into the wall of the stomach. In time, cancer cells can break away and spread to other parts of the body. When cancer cells spread to another part of the body it's called metastasis.

### **Types of stomach cancer**

The type of stomach cancer you have is based on the type of cell where your cancer began. Examples of stomach cancer types include:

* **Adenocarcinoma.** Adenocarcinoma stomach cancer starts in cells that produce mucus. This is the most common type of stomach cancer. Nearly all cancers that start in the stomach are adenocarcinoma stomach cancers.
* **Gastrointestinal stromal tumors (GIST).** GIST starts in special nerve cells that are found in the wall of the stomach and other digestive organs. GIST is a type of soft tissue sarcoma.
* **Carcinoid tumors.** Carcinoid tumors are cancers that start in the neuroendocrine cells. Neuroendocrine cells are found in many places in the body. They do some nerve cell functions and some of the work of cells that make hormones. Carcinoid tumors are a type of neuroendocrine tumor.
* **Lymphoma.** Lymphoma is a cancer that starts in immune system cells. The body's immune system fights germs. Lymphoma can sometimes start in the stomach if the body sends immune system cells to the stomach. This might happen if the body is trying to fight off an infection. Most lymphomas that start in the stomach are a type of non-Hodgkin's lymphoma.

**Risk factors**

Factors that increase the risk of stomach cancer include:

* Ongoing problems with stomach acid backing up into the esophagus, which is called gastroesophageal reflux disease
* A diet high in salty and smoked foods
* A diet low in fruits and vegetables
* Infection in the stomach caused by a germ called Helicobacter pylori
* Swelling and irritation of the inside of the stomach, which is called gastritis
* Smoking
* Growths of noncancerous cells in the stomach, called polyps
* Family history of stomach cancer
* Family history of genetic syndromes that increase the risk of stomach cancer and other cancers, such as hereditary diffuse gastric cancer, Lynch syndrome, juvenile polyposis syndrome, Peutz-Jeghers syndrome and familial adenomatous polyposis

**Symptoms**

Signs and symptoms of stomach cancer may include:

* Trouble swallowing
* Belly pain
* Feeling bloated after eating
* Feeling full after eating small amounts of food
* Not feeling hungry when you would expect to be hungry
* Heartburn
* Indigestion
* Nausea
* Vomiting
* Losing weight without trying
* Feeling very tired
* Stools that look black

Stomach cancer doesn't always cause symptoms in its early stages. When they happen, symptoms might include indigestion and pain in the upper part of the belly. Symptoms might not happen until the cancer is advanced. Later stages of stomach cancer might cause symptoms such as feeling very tired, losing weight without trying, vomiting blood and having black stools.

Stomach cancer that spreads to other parts of the body is called metastatic stomach cancer. It causes symptoms specific to where it spreads. For example, when cancer spreads to the lymph nodes it might cause lumps you can feel through the skin. Cancer that spreads to the liver might cause yellowing of the skin and whites of the eyes. If cancer spreads within the belly, it might cause fluid to fill the belly. The belly might look swollen.

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### **When to see a doctor**

If you have signs and symptoms that worry you, make an appointment with your healthcare provider. Many conditions can cause symptoms that are like the ones caused by stomach cancer. Your provider might test for those other causes first before testing for stomach cancer.

**DIAGNOSIS**

Tests and procedures used to diagnose and detect stomach cancer include:

* **Looking inside the stomach.** To look for signs of cancer, your health care provider might use a tiny camera to see inside your stomach. This procedure is called upper endoscopy. A thin tube with a tiny camera on the end is passed down the throat and into the stomach.
* **Taking a sample of tissue for testing.** If something that looks like cancer is found in your stomach, it might be removed for testing. This is called a biopsy. It can be done during an upper endoscopy. Special tools are passed down the tube to get the tissue sample. The sample is sent to a lab for testing.

### **Determining the stage of stomach cancer**

Once you're found to have stomach cancer, you might have other tests to see if the cancer has spread. This information is used to give the cancer a stage. The stage tells your provider how advanced your cancer is and about your prognosis. Tests and procedures used to find the stage of stomach cancer include:

* **Blood tests.** A blood test can't diagnose stomach cancer. Blood tests can give your provider clues about your health. For example, tests to measure your liver health might show problems caused by stomach cancer that spreads to the liver.  
  Another type of blood test looks for pieces of cancer cells in the blood. This is called a circulating tumor DNA test. It's only used in certain situations for people with stomach cancer. For example, this test might be used if you have advanced cancer and can't have a biopsy. Collecting pieces of cells from the blood can give your health care team information to help plan your treatment.
* **Stomach ultrasound.** Ultrasound is an imaging test that uses sound waves to make pictures. For stomach cancer, the pictures can show how far the cancer has grown into the stomach wall. To get the pictures, a thin tube with a camera on the tip goes down the throat and into the stomach. A special ultrasound tool is used to make pictures of the stomach.  
  Ultrasound might be used to look at lymph nodes near the stomach. The images can help guide a needle to collect tissue from the lymph nodes. The tissue is tested in a lab to look for cancer cells.
* **Imaging tests.** Imaging tests make pictures to help your care team look for signs that stomach cancer has spread. The pictures could show cancer cells in nearby lymph nodes or other parts of the body. Tests may include CT and positron emission tomography (PET).
* **Surgery.** Sometimes imaging tests don't give a clear picture of your cancer, so surgery is needed to see inside the body. Surgery can look for cancer that has spread, which is also called metastasized cancer. Surgery might help your health care team make sure there are no small bits of cancer on the liver or in the belly.

Other tests may be used in certain situations.

Your health care team uses the information from these tests to give your cancer a stage.

**The stages of stomach cancer are numbers from 0 to 4.**

At stage 0, the cancer is small and only on the inside surface of the stomach. A stage 1 stomach cancer has grown into the inner layers of the stomach. In stage 2 and stage 3, the cancer grows deeper into the wall of the stomach. The cancer may have spread to nearby lymph nodes.

At stage 4, the stomach cancer may have grown through the stomach and into nearby organs. Stage 4 includes cancers that have spread to other parts of the body. When cancer spreads, it's called metastatic cancer. When stomach cancer metastasizes, it often goes to the lymph nodes or the liver. It can also go to the lining around the organs in the belly, which is called the peritoneum.

Your health care team might give your cancer a new stage after your first treatment. There are separate staging systems for stomach cancer that can be used after surgery or after chemotherapy.

### **Understanding your prognosis**

Your health care team uses your cancer's stage to understand your prognosis. The prognosis is how likely it is that the cancer will be cured. For stomach cancer, the prognosis for early-stage cancer is very good. As the stage gets higher, the chances of a cure get lower. Even when stomach cancer can't be cured, treatments may control the cancer to prolong your life and make you comfortable.

Things that can influence the prognosis for stomach cancer include:

* The type of cancer
* The cancer's stage
* Where the cancer is within the stomach
* Your overall health
* If the cancer is removed completely with surgery
* If the cancer responds to treatment with chemotherapy or radiation therapy

If you're concerned about your prognosis, talk about it with your provider. Ask about the seriousness of your cancer.

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### **Detecting stomach cancer before it causes symptoms**

**Upper endoscopy**

Sometimes tests are used to look for stomach cancer in people who don't have symptoms. This is called stomach cancer screening. The goal of screening is to detect stomach cancer when it's small and more likely to be cured.

In the United States, stomach cancer screening tests are only for people with a high risk of stomach cancer. Your risk could be high if stomach cancer runs in your family. You could have a high risk if you have a genetic syndrome that can cause stomach cancer. Examples include hereditary diffuse gastric cancer, Lynch syndrome, juvenile polyposis syndrome, Peutz-Jeghers syndrome and familial adenomatous polyposis.

In other parts of the world where stomach cancer is much more common, tests to detect stomach cancer are used more widely.

Upper endoscopy is the most common test used to detect stomach cancer. Some countries use X-rays to detect stomach cancer.

Stomach cancer screening is an active area of cancer research. Scientists are studying blood tests and other ways to detect stomach cancer before it causes symptoms.

**Treatment**

Treatment options for stomach cancer depend on the cancer's location within the stomach and its stage. Your health care provider also thinks about your overall health and your preferences when making a treatment plan. Stomach cancer treatments include surgery, chemotherapy, radiation therapy, targeted therapy, immunotherapy and palliative care.

### **Surgery**

The goal of surgery for stomach cancer, which is also called gastric cancer, is to remove all of the cancer. For small stomach cancers, surgery might be the first treatment. Other treatments might be used first if the stomach cancer grows deeper into the stomach wall or spreads to the lymph nodes.

Operations used to treat stomach cancer include:

* **Removing small cancers from the stomach lining.** Very small cancers can be cut away from the inside lining of the stomach. To remove the cancer, a tube is passed down the throat and into the stomach. Special cutting tools are passed through the tube to cut out the cancer. This procedure is called an endoscopic mucosal resection. It might be an option for treating stage 1 cancer that's growing on the inner lining of the stomach.
* **Removing part of the stomach.** This procedure is called a subtotal gastrectomy. The surgeon removes the part of the stomach affected by cancer and some of the healthy tissue around it. It might be an option if your stomach cancer is located in the part of the stomach nearest the small intestine.
* **Removing the entire stomach.** This procedure is called a total gastrectomy. It involves removing all of the stomach and some surrounding tissue. The surgeon connects the esophagus to the small intestine to allow food to move through the digestive system. Total gastrectomy is a treatment for cancers in the part of the stomach that is closest to the esophagus.
* **Removing lymph nodes to look for cancer.** The surgeon may remove lymph nodes in your belly to test them for cancer.
* **Surgery to relieve symptoms.** An operation to remove part of the stomach may relieve symptoms of a growing cancer. This might be an option if the cancer is advanced and other treatments haven't helped.

Small stage 1 stomach cancers often can be cut away from the inner lining of the stomach. But if the cancer grows into the muscle layer of the stomach wall, this might not be an option. Some stage 1 cancers may need surgery to remove all of or some of the stomach.

For stage 2 and stage 3 stomach cancers, surgery might not be the first treatment. Chemotherapy and radiation therapy might be used first to shrink the cancer. This might make it easier to remove the cancer completely. Surgery often involves removing some or all of the stomach and also some lymph nodes.

If stage 4 stomach cancer grows through the stomach and into nearby organs, surgery might be an option. To remove all of the cancer, parts of the nearby organs might be removed, too. Other treatments might be used first to shrink the cancer. If a stage 4 cancer can't be removed completely, surgery might help control symptoms.

### **Chemotherapy**

Chemotherapy is a drug treatment that uses chemicals to kill cancer cells. Types of chemotherapy include:

* **Chemotherapy that travels through your whole body.** The most common type of chemotherapy involves medicines that travel through your whole body, killing cancer cells. This is called systemic chemotherapy. The medicines can be given through a vein or taken in pill form.
* **Chemotherapy that only goes in the belly.** This type of chemotherapy is called hyperthermic intraperitoneal chemotherapy (HIPEC). HIPEC is done right after surgery. After the surgeon removes the stomach cancer, the chemotherapy medicines are put directly into the belly. The medicines are heated to make them more effective. The chemotherapy is left in place for a set amount of time and then drained.

Chemotherapy might not be needed for stage 1 stomach cancer. It might not be needed if surgery removed all of the cancer and there's a low risk of cancer coming back.

Chemotherapy is often used before surgery to treat stage 2 and stage 3 stomach cancers. Systemic chemotherapy might help shrink the cancer so that it's easier to remove. Giving chemotherapy before surgery is called neoadjuvant chemotherapy.

Systemic chemotherapy might be used after surgery if there's a risk that some cancer cells were left behind. This risk might be higher if the cancer grows deep into the stomach wall or spreads to the lymph nodes. Giving chemotherapy after surgery is called adjuvant chemotherapy.

Chemotherapy can be used alone or it can be combined with radiation therapy.

If surgery isn't an option, systemic chemotherapy might be recommended instead. It might be used if the cancer is too advanced or if you're not healthy enough to have surgery. Chemotherapy might help control cancer symptoms.

HIPEC is an experimental treatment that might be an option for stage 4 stomach cancer. It might be used if the cancer can't be removed completely because it extends through the stomach and into nearby organs. The surgeon might remove as much of the cancer as possible. Then HIPEC helps to kill any cancer cells that are left.

### **Radiation therapy**

Radiation therapy uses high-powered beams of energy to kill cancer cells. The beams can come from X-rays, protons or other sources. During radiation therapy, you lie on a table while a machine gives the radiation treatment to precise points on your body.

Radiation therapy is often done at the same time as chemotherapy. Sometimes doctors call this chemoradiation.

Radiation therapy might not be needed for stage 1 stomach cancer. It might not be needed if surgery removed all of the cancer and there's a low risk that the cancer will come back.

Radiation is sometimes used before surgery to treat stage 2 and stage 3 stomach cancers. It can shrink the cancer so that it's easier to remove. Giving radiation before surgery is called neoadjuvant radiation.

Radiation therapy might be used after surgery if the cancer can't be removed completely. Giving radiation after surgery is called adjuvant radiation.

Radiation can help relieve stomach cancer symptoms if the cancer is advanced or surgery isn't possible.

### **Targeted therapy**

Targeted treatments use medicines that attack specific chemicals present within cancer cells. By blocking these chemicals, targeted treatments can cause cancer cells to die.

Your cancer cells are tested to see if targeted therapy is likely to work for you.

For stomach cancer, targeted therapy is often used with systemic chemotherapy. Targeted therapy is typically used for advanced stomach cancer. This might include stage 4 stomach cancer and cancer that comes back after treatment.

### **Immunotherapy**

Immunotherapy is a treatment with medicine that helps your body's immune system to kill cancer cells. Your immune system fights off diseases by attacking germs and other cells that shouldn't be in your body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells.

Immunotherapy is sometimes used to treat advanced cancer. This might include stage 4 stomach cancer or cancer that comes back after treatment.

### **Palliative care**

Palliative care is a special type of health care that helps you feel better when you have a serious illness. If you have cancer, palliative care can help relieve pain and other symptoms. Palliative care is done by a team of healthcare providers. This can include doctors, nurses and other specially trained professionals. Their goal is to improve the quality of life for you and your family.

Palliative care specialists work with you, your family and your care team to help you feel better. They provide an extra layer of support while you have cancer treatment. You can have palliative care at the same time as strong cancer treatments, such as surgery, chemotherapy or radiation therapy.

When palliative care is used along with all of the other appropriate treatments, people with cancer may feel better and live longer.

**Prevention**

To lower the risk of stomach cancer, you can:

* **Eat plenty of fruits and vegetables.** Try to include fruits and vegetables in your diet each day. Choose a variety of colorful fruits and vegetables.
* **Reduce the amount of salty and smoked foods you eat.** Protect your stomach by limiting these foods.
* **Stop smoking.** If you smoke, quit. If you don't smoke, don't start. Smoking increases your risk of stomach cancer and many other types of cancer. Quitting smoking can be very hard, so ask your health care provider for help.
* **Tell your healthcare provider if stomach cancer runs in your family.** People with a strong family history of stomach cancer might have stomach cancer screening. Screening tests can detect stomach cancer before it causes symptoms.

## **Epidemiology**

### United States

The American Cancer Society estimates that about 30,300 cases of stomach cancer (17,720 in men and 12,580 in women) will be diagnosed in 2025.Median age at diagnosis is 68 years. From 2012–2021, the rate of new stomach cancer cases has been relatively stable. Gastric cancer is the 15th most common cancer in the US.

### International

Once the second most common cancer worldwide, stomach cancer has dropped to sixth place, after cancers of the female breast, lung, colon and rectum, and prostate.Stomach cancer is the fourth most common cause of death from cancer. The World Health Organization estimates that in 2022, gastric cancer accounted for 660,175 deaths worldwide. [1]

Tremendous geographic variation exists in the incidence of this disease around the world. Rates of the disease are low in Africa, North America, and northern Europe, and highest in eastern Asia (eg, Mongolia, Japan, the Republic of Korea) and eastern Europe. The highest death rates are recorded in south central Asian countries, including Iran, Afghanistan, Turkmenistan, and Kyrgyzstan.

Using data from 92 cancer registries in 34 countries representing 10 world regions, Arnold et al predicted that overall gastric cancer incidence rates will continue falling in most countries, including high-incidence countries such as Japan as well as low-incidence ones such as Australia. By 2035, incidence rates in 16 of those 34 countries will fall below the rare disease threshold (defined as 6 per 100,000 person-years).

Nevertheless, the absolute number of new gastric cancer cases is expected to increase in the majority of countries. New cases could double in Canada, Cyprus, South Korea, Slovakia, and Thailand, while dropping slightly in a few other countries (eg, Bulgaria, Lithuania).

While decreasing or stable incidence rates were consistently observed in people aged 50 years and above, Arnold et al predicted increases in incidence in those younger than 50 years in 15 of 34 countries, including Belarus, Chile, the Netherlands, Canada, and the United Kingdom.

## 

## **Staging**

TNM classification system for staging gastric carcinoma:

### Primary tumor (T)

See the list below:

* TX - Primary tumor cannot be assessed
* T0 - No evidence of primary tumor
* Tis - Carcinoma in situ, intraepithelial tumor without invasion of lamina propria
* T1 - Tumor invades lamina propria, muscularis mucosae, or submucosa
* T1a - Tumor invades lamina propria or muscularis mucosae
* T1b - Tumor invades submucosa
* T2 - Tumor invades muscularis propria
* T3 - Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
* T4 - Tumor invades serosa (visceral peritoneum) or adjacent structures
* T4a - Tumor invades serosa (visceral peritoneum)
* T4b - Tumor invades adjacent structures/organs

### Regional lymph nodes (N)

See the list below:

* NX - Regional lymph node(s) cannot be assessed
* N0 - No regional lymph node metastases
* N1 - Metastases in 1-2 regional lymph nodes
* N2 - Metastases in 3-6 regional lymph nodes
* N3 - Metastases in 7 or more regional lymph nodes
* N3a - Metastases in 7-15 regional lymph nodes
* N3b - Metastases in 16 or more regional lymph nodes

### Distant metastasis

See the list below:

* M0 - No distant metastasis
* M1 - Distant metastasis

### Prognostic features

Two important factors influencing survival in resectable gastric cancer are depth of cancer invasion through the gastric wall and presence or absence of regional lymph node involvement.

In about 5% of primary gastric cancers, a broad region of the gastric wall or even the entire stomach is extensively infiltrated by malignancy, resulting in a rigid thickened stomach, termed linitis plastica. Patients with linitis plastica have an extremely poor prognosis.

Margins positive for presence of cancer are associated with a very poor prognosis.

The greater the number of involved lymph nodes, the more likely the patient is to develop local and systemic failure after surgery.

In a study by Shen and colleagues,the depth of tumor invasion and gross appearance, size, and location of the tumor were 4 pathologic factors independently correlated with the number of metastatic lymph nodes associated with gastric cancer.

Lee and colleagues found that surgical stage, as estimated during curative resection for gastric cancer, complemented the pathologically determined stage for determining prognosis. Survival was significantly poorer among patients with pathologic Stages II, IIIa, and IIIb disease in whom intraoperative staging overestimated the extent of pathological stage.

### Clinical Staging

See the list below:

* Stage 0 - Tis, N0, M0
* Stage I - T1-2, N0, M0
* Stage IIA - T1-2, N1-3, M0
* Stage IIB - T3, N0, M0 or T4a, N0, M0
* Stage III - T3, N0, M0 or; T4a, N1-3, M0
* Stage IVA - T4b, any N, M0
* Stage IVB - Any T, any N, M1

### Survival rates

See the list below:

* Stage IA - 94%
* Stage IB - 88%
* Stage IIA - 82%
* Stage IIB - 68%
* Stage IIIA - 54%
* Stage IIIB - 36%
* Stage IIIC - 18%
* Stage IV - 5%

### **Spread patterns**

Cancer of the stomach can spread directly, via lymphatics, or hematogenously. Features of spread include the following:

* Direct extension into the omenta, pancreas, diaphragm, transverse colon or mesocolon, and duodenum is common
* If the lesion extends beyond the gastric wall to a free peritoneal (ie, serosal) surface, then peritoneal involvement is frequent
* The visible gross lesion frequently underestimates the true extent of the disease
* The abundant lymphatic channels within the submucosal and subserosal layers of the gastric wall allow for easy microscopic spread
* The submucosal plexus is prominent in the esophagus and the subserosal plexus is prominent in the duodenum, allowing proximal and distal spread
* Lymphatic drainage is through numerous pathways and can involve multiple nodal groups (eg, gastric, gastroepiploic, celiac, porta hepatic, splenic, suprapancreatic, pancreaticoduodenal, paraesophageal, and paraaortic lymph nodes)
* Hematogenous spread commonly results in liver metastases

For systemic therapy, NCCN recommendations are as follows:

* Perioperative chemotherapy - Preferred regimens are FLOT (fluorouracil, leucovorin, oxaliplatin, docetaxel [Taxotere]) (category 1) and a fluoropyrimidine plus oxaliplatin
* Preoperative chemoradiation - Infusional fluorouracil can be replaced with capecitabine
* Postoperative chemoradiation in patients who received less than a D2 lymph node dissection - Infusional fluorouracil or capecitabine before and after fluoropyrimidine-based chemoradiation
* Postoperative chemoradiation in patients who have undergone primary D2 lymph node dissection - Preferred regimens are capecitabine and oxaliplatin (category 1) and fluorouracil and oxaliplatin
* Chemoradiation for unresectable disease - Preferred Regimens are fluorouracil (or capecitabine) and either oxaliplatin or cisplatin

***Local and locoregional gastric cancer:***

* Endoscopic or surgical resection alone is appropriate for selected very early tumors (stage IA).
* For stage IB-III gastric cancer, perioperative therapy and radical gastrectomy is recommended.
* Preoperative and postoperative chemotherapy is recommended for patients with stage ≥IB resectable gastric cancer.
* A triplet chemotherapy regimen including a fluoropyrimidine, a platinum compound, and docetaxel should be given when possible.
* Perioperative use of FLOT is standard of care for patients who are able to tolerate a triple cytotoxic drug regimen.
* For patients unfit for triplet chemotherapy, a combination of a fluoropyrimidine with cisplatin or oxaliplatin is recommended.

*Adjuvant treatment of local and locoregional disease:*

* For patients with stage ≥IB gastric cancer who have undergone surgery without preoperative chemotherapy, adjuvant chemotherapy is recommended.
* For patients who have undergone surgery with clear margins (R0), postoperative radiation therapy (RT) has no added benefit and should not be given.
* For patients who receive preoperative or postoperative chemotherapy, the addition of postoperative RT has no added benefit and should not be given.
* For patients who have not received preoperative chemotherapy and have not undergone an appropriate D2 lymphadenectomy, adjuvant chemoradiation therapy (CRT) can be considered.
* For patients who have undergone surgery with involved margins (R1), adjuvant RT or CRT might be considered as an individual recommendation, but is not standard.
* For patients with high microsatellite instability (MSI-H) gastric cancer who have undergone curative surgery, adjuvant chemotherapy cannot be recommended, but if a response is required to downstage a tumor before surgery, FLOT is recommended.

***Treatment of locally advanced unresectable or metastatic gastric cancer:***

* First-line chemotherapy with platinum and fluoropyrimidine is recommended. Oxaliplatin is preferred, especially for older patients. Tegafur–gimeracil–oteracil (S-1) is commonly used in Asian patients.
* Due to higher levels of toxicity and uncertain survival benefit over recommended doublet regimens, first-line taxane-based triplet chemotherapy is not recommended as a standard approach.
* Irinotecan–5-fluorouracil (5-FU) can be considered an alternative option for patients who do not tolerate platinum compounds.
* Trastuzumab plus chemotherapy is recommended in patients with HER2-positive tumors.
* Nivolumab plus chemotherapy is recommended for advanced untreated gastric, esophagogastric junction, and esophageal cancer with a programmed death ligand 1 (PD-L1) combined positive score (CPS) ≥5.
* Pembrolizumab is approved for patients with esophagogastric junction adenocarcinoma that expresses PD-L1 CPS ≥10.

*Second- and later-line treatment for locally advanced unresectable or metastatic gastric cancer:*

* Ramucirumab–paclitaxel is recommended for second-line treatment of gastric. Ramucirumab monotherapy is also an option.
* Where ramucirumab is not available, paclitaxel, docetaxel, or irinotecan monotherapy or FOLFIRI are recommended.
* Treatment with trastuzumab is not recommended after first-line therapy in HER2-positive advanced gastric cancer but trastuzumab deruxtecan may be considered (Food and Drug Administration [FDA] approved, not European Medicines Agency [EMA] approved).
* Pembrolizumab is recommended for second-line treatment of patients with MSI-H/deficient mismatch repair (dMMR) gastric cancer.
* For patients previously treated with two lines of therapy, trifluridine–tipiracil is recommended. Alternative treatments include a taxane or irinotecan.

*Surgery for metastatic gastric cancer:*

* Gastrectomy is not recommended in metastatic gastric cancer unless required for palliation of symptoms.
* Resection of metastases cannot be recommended in general, but might be considered as an individual approach in highly selected patients with oligometastatic disease and response to chemotherapy.

**Differential diagnoses** that should be considered when evaluating gastric cancer include:

* Acute gastritis
* Atrophic gastritis
* Bacterial gastroenteritis
* Chronic gastritis
* Esophageal cancer
* Esophageal stricture
* Esophagitis
* Non-Hodgkin lymphoma
* Peptic ulcer disease
* Viral gastroenteritis

## **Genomic Data of Gastric (Stomach) Cancer**

## Key Genomic Alterations

* CDH1 Mutations (E-cadherin gene):
  + Germline mutations in the *CDH1* gene are the primary cause of hereditary diffuse gastric cancer (HDGC), accounting for 1–3% of all gastric cancers.
  + *CDH1* mutations lead to loss of cell adhesion, contributing to the diffuse type of gastric cancer, which is often diagnosed late due to its subtle growth pattern.
  + Families with multiple cases of diffuse gastric cancer, especially at young ages, are referred for *CDH1* genetic testing.
* Other Hereditary Genes:
  + *PALB2*, *MSH2*, and *RECQL5* have been implicated as potential susceptibility genes for hereditary gastric cancer, but their roles are less well established than *CDH1*.
  + *BRCA1* and *BRCA2* mutations, while primarily associated with breast and ovarian cancers, have also been linked to a modestly increased risk of gastric cancer.
* Somatic (Tumor-Acquired) Mutations:
  + The majority of gastric cancers are sporadic and result from somatic mutations acquired over a person’s lifetime.
  + Commonly mutated genes in sporadic gastric cancer include:
    - *TP53*, *CDH1*, *SMAD4*, *PIK3CA*, *RHOA*, *ARID1A*, *KRAS*, *APC*, *ERBB1* (EGFR), *PTEN*, and others.
    - *CTNNB1* (beta-catenin) mutations are more frequent in intestinal-type gastric cancers.
    - Loss of heterozygosity, microsatellite instability, and chromosomal instability are frequent molecular events

## **Doctor-Patient Conversation: Gastric (Stomach) Cancer**

Doctor: Thank you for coming in today. I have your test results, and I’d like to talk through them with you. The diagnosis is gastric cancer, also known as stomach cancer.

Patient: That’s a lot to process. What does this mean for me?

Doctor: I understand this is difficult news. The first thing we need to do is determine the stage of your cancer—meaning how far it has spread, whether it’s confined to the stomach or has involved other organs like the liver, lungs, or lymph nodes. This information is crucial because it guides our treatment plan and helps us discuss your outlook.

Patient: What are my treatment options?

Doctor: Treatment depends on the stage and your overall health. If the cancer is localized and small, sometimes it can be removed with a special endoscopy procedure. If it’s more advanced but still contained, surgery to remove part or all of the stomach may be recommended, often combined with chemotherapy or radiation. For cancer that has spread further, chemotherapy and sometimes targeted therapies or clinical trials are options to help control the disease and manage symptoms.

Patient: What side effects might I have from treatment?

Doctor: Side effects depend on the treatment. Surgery can cause pain, changes in digestion, or weight loss. Chemotherapy may cause fatigue, nausea, or increased risk of infection. Radiation can cause tiredness and digestive symptoms. We’ll help you manage any side effects to support your recovery and quality of life.

Patient: Are there clinical trials I should consider?

Doctor: Yes, there are clinical trials for many stages of gastric cancer. These may offer access to new treatments. We can discuss whether you’re eligible and what might be involved.

Patient: Will I be able to keep working or doing my daily activities?

Doctor: Many people can continue some daily activities, but treatment may cause fatigue or other side effects. We’ll work together to support your quality of life and make adjustments as needed.

Patient: Where can I find support?

Doctor: Our cancer center has social workers and support groups for emotional and practical support. National organizations and online communities can also connect you with others going through similar experiences.

Patient: What should I do to stay as healthy as possible?

Doctor: Eat a balanced diet, stay as active as you can, and let us know about any new symptoms. Emotional well-being is also important, so please reach out if you need support. We’ll be here to guide you at every step.

Doctor: Please write down any questions you have and bring them to our next visit. We’re here to support you throughout your treatment and beyond.

## **Outlook / Prognosis**

Stomach cancer can be cured if it’s in the early stages. Often, though, diagnosis happens in later stages once symptoms begin. Ask your provider about the factors that play a role in your treatment outcomes.

### **What is the prognosis (outlook) for people who have stomach cancer?**

The outlook for stomach cancer depends on the stage of cancer. People in the early stages of stomach cancer have a much better prognosis than those at a later stage. The 5-year survival rate for stomach cancer may be as high as 70% (for little spread) or as low as 6% (for advanced spread).

Speak with your provider for a more accurate assessment of your prognosis. The type of cancer you have, its spread, your health and how your cancer responds to treatment all shape your prognosis.

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**COLON CANCER**

**DEFINITION AND DESCRIPTION**

Colon cancer is a growth of cells that begins in a part of the large intestine called the colon. The colon is the first and longest part of the large intestine. The large intestine is the last part of the digestive system. The digestive system breaks down food for the body to use.

Colon cancer typically affects older adults, though it can happen at any age. It usually begins as small clumps of cells called polyps that form inside the colon. Polyps generally aren't cancerous, but some can turn into colon cancers over time.

Polyps often don't cause symptoms. For this reason, doctors recommend regular screening tests to look for polyps in the colon. Finding and removing polyps helps prevent colon cancer.

If colon cancer develops, many treatments can help control it. Treatments include surgery, radiation therapy and medicines, such as chemotherapy, targeted therapy and immunotherapy.

Colon cancer is sometimes called colorectal cancer. This term combines colon cancer and rectal cancer, which begins in the rectum.

**Causes**

Doctors aren't certain what causes most colon cancers.

Colon cancer happens when cells in the colon develop changes in their DNA. A cells' DNA holds the instructions that tell the cell what to do. The changes tell the cells to multiply quickly. The changes let the cells continue living when healthy cells die as part of their natural lifecycle.

This causes too many cells. The cells might form a mass called a tumor. The cells can invade and destroy healthy body tissue. In time, the cells can break away and spread to other parts of the body. When cancer spreads, it's called metastatic cancer.

**Risk factors**

Factors that may increase the risk of colon cancer include:

* **Older age.** Colon cancer can happen at any age. But most people with colon cancer are older than 50. The numbers of people younger than 50 who have colon cancer has been growing. Doctors don't know why.
* **Black race.** Black people in the United States have a greater risk of colon cancer than do people of other races.
* **A personal history of colorectal cancer or polyps.** Having had colon cancer or colon polyps increases the risk of colon cancer.
* **Inflammatory bowel diseases.** Conditions that cause pain and swelling of the intestines, called inflammatory bowel diseases, can increase the risk of colon cancer. These conditions include ulcerative colitis and Crohn's disease.
* **Inherited syndromes that increase colon cancer risk.** Some DNA changes that increase the risk of colon cancer run in families. The most common inherited syndromes that increase colon cancer risk are familial adenomatous polyposis and Lynch syndrome.
* **Family history of colon cancer.** Having a blood relative who has colon cancer increases the risk of getting colon cancer. Having more than one family member who has colon cancer or rectal cancer increases the risk more.
* **Low-fiber, high-fat diet.** Colon cancer and rectal cancer might be linked with a typical Western diet. This type of diet tends to be low in fiber and high in fat and calories. Research in this area has had mixed results. Some studies have found an increased risk of colon cancer in people who eat a lot of red meat and processed meat.
* **Not exercising regularly.** People who are not active are more likely to develop colon cancer. Getting regular physical activity might help lower the risk.
* **Diabetes.** People with diabetes or insulin resistance have an increased risk of colon cancer.
* **Obesity.** People who are obese have an increased risk of colon cancer. Obesity also increases the risk of dying of colon cancer.
* **Smoking.** People who smoke can have an increased risk of colon cancer.
* **Drinking alcohol.** Drinking too much alcohol can increase the risk of colon cancer.
* **Radiation therapy for cancer.** Radiation therapy directed at the abdomen to treat previous cancers increases the risk of colon cancer.

**Symptoms**

Many people with colon cancer don't have symptoms at first. When symptoms appear, they'll likely depend on the cancer's size and where it is in the large intestine.

Symptoms of colon cancer can include:

* A change in bowel habits, such as more frequent diarrhea or constipation.
* Rectal bleeding or blood in the stool.
* Ongoing discomfort in the belly area, such as cramps, gas or pain.
* A feeling that the bowel doesn't empty all the way during a bowel movement.
* Weakness or tiredness.
* Losing weight without trying.

### **When to see a doctor**

If you notice lasting symptoms that worry you, make an appointment with a health care professional.

## **Diagnosis**

### **Diagnosing colon cancer**

### Colonoscopy exam

## Tests and procedures used for colon cancer diagnosis include:

## Using a scope to examine the inside of the colon. Colonoscopy uses a long, flexible and slender tube attached to a video camera and monitor to view the whole colon and rectum. A doctor may pass surgical tools through the tube to take tissue samples and remove polyps.

## Removing a sample of tissue for testing. A biopsy is a procedure to remove a sample of tissue for testing in a lab. For colon cancer, the tissue sample is often collected during a colonoscopy. Sometimes surgery is needed to get the tissue sample. In the lab, tests can show whether the cells are cancerous and how quickly they're growing. Other tests can give more information about the cancer cells. Your health care team uses the results to understand your prognosis and create a treatment plan.

## Blood tests. Blood tests aren't used to diagnose colon cancer. But blood tests can give clues about overall health, such as how well the kidneys and liver are working. A blood test might be used to look for a low level of red blood cells. This result might indicate that a colon cancer is causing bleeding. Colon cancers sometimes make a protein called carcinoembryonic antigen, also called CEA. Blood tests can track the level of CEA over time. The results might show whether the cancer is responding to treatment. After treatment, CEA blood tests might detect if the cancer comes back.

## 

## **Colon cancer stages**

## After a colon cancer diagnosis, other tests might be needed to find out the extent of the cancer. This is called the cancer's stage. The health care team considers the cancer's stage when creating a treatment plan.

## Staging tests might include imaging scans of the abdomen, pelvis and chest. Imaging tests take pictures of the body. They show the location and the size of the colon cancer. Often, doctors can't be certain of the cancer's stage until after colon cancer surgery.

## Colon cancer stages range from 0 to 4. The lowest numbers mean the cancer is all inside the lining of the colon. By stage 4, the cancer is considered advanced and has spread to other areas of the body. When cancer spreads, it's called metastatic cancer.

## 

## **Prevention**

### **Screening for colon cancer**

Doctors recommend that people with an average risk of colon cancer consider starting colon cancer screening around age 45. But people with an increased risk should think about starting screening sooner. People with an increased risk include those with a family history of colon cancer.

There are several different tests that are used for colon cancer screening. Talk about your options with your health care team.

### 

### **Lifestyle changes to reduce the risk of colon cancer**

Making changes in everyday life can reduce the risk of colon cancer. To lower the risk of colon cancer:

* **Eat a variety of fruits, vegetables and whole grains.** Fruits, vegetables and whole grains have vitamins, minerals, fiber and antioxidants, which may help prevent cancer. Choose a variety of fruits and vegetables so that you get a range of vitamins and nutrients.
* **Drink alcohol in moderation, if at all.** If you choose to drink alcohol, limit the amount you drink to no more than one drink a day for women and two for men.
* **Stop smoking.** Talk to your health care team about ways to quit.
* **Exercise most days of the week.** Try to get at least 30 minutes of exercise on most days. If you've been inactive, start slowly and build up gradually to 30 minutes. Also, talk with a health care professional before starting an exercise program.
* **Maintain a healthy weight.** If you are at a healthy weight, work to maintain your weight by combining a healthy diet with daily exercise. If you need to lose weight, ask your health care team about healthy ways to achieve your goal. Aim to lose weight slowly by eating fewer calories and moving more.

### **Colon cancer prevention for people with a high risk**

Some medicines can reduce the risk of colon polyps or colon cancer. For instance, some evidence links a reduced risk of polyps and colon cancer to regular use of aspirin or aspirin-like medicines. But it's not clear what dose and what length of time would be needed to reduce the risk of colon cancer. Taking aspirin daily has some risks, including ulcers and bleeding in the digestive system.

These options are generally reserved for people with a high risk of colon cancer. There isn't enough evidence to recommend these medicines to people who have an average risk of colon cancer.

If you have an increased risk of colon cancer, discuss your risk factors with your health care team to see if preventive medicines are safe for you.

**Treatment**

Colon cancer treatment usually involves surgery to remove the cancer. Your health care team might recommend other treatments, such as radiation therapy and chemotherapy. Your treatment options depend on the cancer's location and its stage. Your health care team also considers your overall health and your preferences when creating a treatment plan.

### **Surgery for early-stage colon cancer**

Treatment for a very small colon cancer might be a minimally invasive approach to surgery, such as:

* **Removing polyps during a colonoscopy, called a polypectomy.** If the cancer is contained within a polyp, removing the polyp may remove all of the cancer.
* **Endoscopic mucosal resection.** This procedure can remove larger polyps during colonoscopy. Special tools help remove the polyp and a small amount of the lining of the colon.
* **Minimally invasive surgery, called laparoscopic surgery.** This type of surgery can remove polyps that can't be removed during a colonoscopy. In this procedure, a surgeon performs the operation through several small cuts called incisions in the abdominal wall. Instruments with attached cameras go through the cuts and show the colon on a video monitor. The surgeon also may take samples from lymph nodes in the area around the cancer.

### **Surgery for more advanced colon cancer**

**Colostomy**

If the cancer has grown into or through the colon, a surgeon might recommend:

* **Partial colectomy.** Surgery to remove part of the colon is called partial colectomy. During this procedure, the surgeon removes the part of the colon that has the cancer. The surgeon also takes some tissue on either side of the cancer. It's often possible to reconnect the healthy portions of the colon or rectum. This procedure can often be done by a minimally invasive approach called laparoscopy.
* **Surgery to create a way for waste to leave the body.** Sometimes it's not possible to reconnect the healthy portions of the colon or rectum after colectomy. The surgeon creates an opening in the wall of the abdomen from a portion of what's left of the intestine. This procedure, called an ostomy, allows stool to leave the body by emptying into a bag that fits over the opening.  
  Sometimes the ostomy is only for a short time to let the colon or rectum heal after surgery. Then it's reversed. Sometimes the ostomy can't be reversed and stays for life.
* **Lymph node removal.** Nearby lymph nodes are usually removed during colon cancer surgery and tested for cancer.

### **Surgery for advanced cancer**

When it's not possible to remove the cancer with surgery, a surgeon might try to relieve symptoms rather than cure the cancer. This surgery can remove colon blockages and ease symptoms, such as bleeding or pain.

Sometimes the cancer has spread only to the liver or lung in someone who is otherwise healthy. Surgery or other localized treatments might remove the cancer. Chemotherapy might be used before or after this type of procedure. This approach provides a chance to be free of cancer over the long term.

### **Chemotherapy**

Chemotherapy uses strong medicines to kill cancer cells. Chemotherapy for colon cancer is usually given after surgery if the cancer is large or has spread to the lymph nodes. Chemotherapy can kill cancer cells that might be left after surgery. This helps reduce the risk of the cancer coming back.

Chemotherapy might also be used before surgery to shrink a large cancer so that it's easier to remove.

Chemotherapy also can be used to relieve symptoms of colon cancer that can't be removed with surgery or that has spread to other areas of the body. Sometimes it's used with radiation therapy.

### **Radiation therapy**

Radiation therapy uses powerful energy beams to kill cancer cells. The energy can come from X-rays, protons or other sources.

Radiation therapy can shrink a large cancer before an operation to make it easier to remove. When surgery isn't an option, radiation therapy might be used to relieve symptoms, such as pain. Some people have radiation and chemotherapy at the same time.

### **Targeted therapy**

Targeted therapy uses medicines that attack certain chemicals in cancer cells. By blocking these chemicals, targeted treatments can cause cancer cells to die.

Targeted therapy is usually combined with chemotherapy. Targeted therapy is typically used for people with advanced colon cancer.

### **Immunotherapy**

Immunotherapy is a treatment with medicine that helps the body's immune system kill cancer cells. The immune system fights off diseases by attacking germs and other cells that shouldn't be in the body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells.

Immunotherapy is usually reserved for advanced colon cancer.

### **Palliative care**

Palliative care is a special type of health care that focuses on relieving pain and other symptoms of a serious illness. Palliative care is done by a team of healthcare professionals. The team can include doctors, nurses and other specially trained professionals. Their goal is to improve the quality of life for people with serious illnesses and their families.

Palliative care is an extra layer of support during cancer treatment. When palliative care is used with all other appropriate treatments, people with cancer may feel better and live longer.

## **Diagnostic Considerations**

Other problems to be considered in the differential diagnosis of colon cancer include the following:

* Arteriovenous malformation (AVM)
* Carcinoid/neuroendocrine tumors and rare tumors of the gastrointestinal tract
* Ischemic bowel
* Small-intestine carcinomas
* Gastrointestinal lymphoma

## **Differential Diagnoses**

* Crohn Disease
* Ileus
* Small Intestinal Diverticulosis
* Ulcerative Colitis

## 

## **Epidemiology**

The incidence and mortality from colon cancer have been on a slow decline over the past several decades in the United States, with the incidence falling on average 2.4% each year and death rates falling on average 2.2% each year over 2007-2019. However, the overall decline has been driven by a decreasing incidence in individuals age 65 years and older; rates have stabilized in those age 55-64 and have increased by 1% to 2% per year since the mid-1990s in those younger than 55 years of age.

Colorectal cancers remain the third most common cancer in US men and women, the third most common cause of cancer-related mortality in US men, and the fourth most common cause of cancer-related mortality in women. The American Cancer Society estimates that 107,320 new cases of colon cancer will be diagnosed in the United States in 2025. Estimates for mortality from colon and rectal cancer (the two are combined because of classification difficulties) are for 52,900 deaths in 2025.

Worldwide, colon cancer was the fourth most common cancer, with an estimated 1,142,286 million new cases in 2022, and the fifth most common cause of cancer mortality, with 538,167 deaths. Geographically, the incidence varies as much as 10-fold. The highest estimated rates are in Australia–New Zealand, Europe, and Northern America, and the lowest in south-central Asia and middle Africa. Mortality rates worldwide vary six-fold, with the highest estimated mortality rates in southern and eastern Europe and the lowest in south-central Asia and middle Africa.

An epidemiologic study from the European Union (EU) concluded that in 2018, colorectal cancer would account for the second highest number of cancer deaths, at 98,000 deaths in men and 79,400 in women. However, while the total number of colorectal deaths in the EU has risen since 2012 because of the aging population, since 2012 the age-standardized death rate has fallen by 6.7% (to 15.8 per 100,000 in men and 7.5% (to 9.2 per 100,000) in women.

A study by Sung et al that examined colorectal cancer incidence trends in younger adults versus older adults in 50 countries and territories found that from 2013 to 2017, early-onset colorectal cancer (diagnosed at ages 25 to 49 years) increased in 27 countries. The greatest annual increases occurred in New Zealand (3.97%), Chile (3.96%), Puerto Rico (3.81%), and England (3.59%). In 14 of those 27 countries and territories, rates in older adults were either stable or decreased.

### Racial, sexual, and age-related disparities in incidence

Since 1989, colorectal cancer incidence rates have been higher for Blacks than for Whites in both men and women. Currently, incidence rates of colorectal cancer are 21% higher in Black men and 18% higher in Black women compared with White men and women, respectively.

Colorectal mortality rates are 44% higher in Black men and 31% higher in Black women compared with White men and women. However, from 2010 to 2019, colorectal cancer death rates declined faster in Blacks than in Whites (2.8% vs 1.8% per year), narrowing the racial disparity in both men and women.

Asians/Pacific Islanders have the lowest incidence and mortality from colorectal cancer. Hispanics have the second lowest. [30]

The incidence of colorectal cancer is relatively equal in men and women. The American Cancer Society estimates that colon cancer will be diagnosed in 54,510 men and 52,810 women in the United States in 2025. [31]

Age is a well-known risk factor for colorectal cancer, as it is for many other solid tumors. The timeline for progression from early premalignant lesion to malignant cancer ranges from 10-20 years. Median age at diagnosis is 66 years.

However, in contrast to the decline in colon cancer incidence rates in persons age 55 and older, which began in the mid-1980s, rates of colon cancer in younger persons have been increasing. In adults age 20 to 39 years, colon cancer incidence rates have increased by 1.0% to 2.4% annually since the mid-1980s; in those age 40 to 54 years, the incidence has increased by 0.5% to 1.3% annually since the mid-1990s. Currently, adults born circa 1990 have double the risk of colon cancer compared with those born circa 1950. Increased obesity is one likely factor.

From 2011 through 2016, the incidence of colorectal cancer continued to decline in those aged 65 years and older, by 3.3% annually. Rates increased by 1% annually in those aged 50 to 64 years, and rose approximately 2% annually in those younger than 50 years. The American Cancer Society estimated that 17,930 of the 147,950 individuals expected to be diagnosed with colon and rectal cancer in 2020, and 3640 of the 53,200 expected to die from the disease, would be younger than 50 years of age.

Tumor site tends to vary by patient age. From 2012 to 2016, the proximal colon was the site of colon cancer in 23% of those under 50 years of age, 31% of those 50-64 years, and 49% of those 65 and older. Incidence trends varied by race/ethnicity: in those 50-64 years old, rates increased in Whites by 1.3% per year but decreased in Blacks by 1.6% per year, and were stable in Hispanics. In those younger than 50, rates rose by 2% annually in Whites and by 0.5% annually in Blacks.

A review of Surveillance, Epidemiology and End Results (SEER) data found that US cases of colorectal cancer in persons aged 40-49 years have increased significantly since 1995, with the greatest average annual percentage increase for distant cancers, at 2.9%, while localized and regional disease each increased < 1.5% per year. In addition, the proportion of distant colorectal cancers in this age group increased significantly from 1990-1994 to 2011–2015, from 22% to 27%, while the proportion of localized cases did not change, and the proportion of regional cases decreased. These authors point out that these results indicate a true increase in risk, because if the increase had reflected earlier detection due to wider use of screening, an earlier stage at diagnosis would be expected.

## **Outlook / Prognosis**

According to U.S. National Cancer Institute (NCI) data, more than 90% of people treated for early-stage colorectal cancer were alive five years after diagnosis. (NCI data doesn’t break out separate survival rates for colon and rectal cancer.)

#### **What are the survival rates for colon cancer?**

NCI data shows that overall, 65% of people with colorectal cancer were alive five years after diagnosis. (A survival rate is an estimate based on the experiences of people with specific kinds of cancer.)

Colorectal cancer survival rates vary based on the cancer stage at diagnosis. For example, 73% of people with colorectal cancer that’s spread to nearby tissues, organs or lymph nodes were alive five years after diagnosis. That five-year survival rate drops to 17% if the cancer spreads to a distant organ or lymph node.

A survival rate is an estimate based on outcomes — how long people lived after treatment for a specific type of cancer. In this case, survival rates are based on the experiences of large groups of people who have colorectal cancer, and not just colon cancer. In addition, many things affect colon cancer survival rates. If you have this condition, your healthcare provider is your best resource for information about what you can expect.

## **Living With**

### **I have colon cancer. How do I take care of myself?**

Self-care is an important part of living with colon cancer, but everyone’s situation is different. People treated for early-stage colon cancer may become cancer-free. They’re cancer survivors, but they may worry that their colon cancer will come back.

People who have advanced colon cancer have different concerns. They’re also cancer survivors. But for them, living with colon cancer may mean treatment that eases symptoms but doesn’t cure colon cancer. They may benefit from having palliative care. Palliative care helps people manage cancer symptoms and treatment side effects.

**COMMON QUESTIONS AND ANSWERS SET**

## What kind of colon cancer do I have?

The vast majority of colon cancers (about 95%) are adenocarcinomas, which develop from the cells lining the inside of the colon. There are rarer types, including carcinoid tumors, gastrointestinal stromal tumors, lymphomas, and squamous cell carcinomas. Your doctor will confirm the specific type based on a biopsy and pathology review.

## Can you cure this kind of colon cancer?

Many cases of colon cancer can be cured, especially if detected at an early stage. The chance of cure depends on the type, stage, and your overall health. Early-stage adenocarcinomas are often curable with surgery, sometimes combined with chemotherapy or radiation.

## What is the cancer stage?

Colon cancer is staged using the TNM (Tumor, Node, Metastasis) system, which assesses how deeply the tumor has invaded the colon wall, whether lymph nodes are involved, and whether there is spread to other organs. Staging determines your treatment plan and prognosis.

## What are effective colon cancer treatments?

* Surgery is the main treatment for most early-stage colon cancers.
* Chemotherapy may be used before or after surgery, especially for more advanced stages.
* Radiation therapy is less common but may be used in certain situations.
* Targeted therapies and immunotherapies may be options for some patients, depending on genetic testing and cancer subtype.

## If I need surgery, what kind of surgery do you recommend?

The type of surgery depends on the tumor’s location and size. Most patients undergo a partial colectomy (removal of the cancerous section of the colon and nearby lymph nodes). Minimally invasive (laparoscopic) techniques are often possible.

## Will I need a colostomy?

A colostomy (an opening of the colon to the abdominal wall) is rarely needed for colon cancer, but it may be necessary if the tumor is low in the rectum or if complications arise. Your surgeon will discuss this possibility with you based on your case.

## Will I need other kinds of cancer treatments?

You may need chemotherapy or, less commonly, radiation therapy after surgery, especially if the cancer has spread to lymph nodes or is at a more advanced stage. Some patients may be eligible for targeted therapy or immunotherapy based on specific genetic features of their tumor.

## What are those treatment side effects?

* Surgery: Pain, infection, changes in bowel habits.
* Chemotherapy: Fatigue, nausea, hair loss, increased infection risk.
* Radiation: Fatigue, skin changes, bowel irritation.
* Targeted therapy/immunotherapy: Side effects depend on the specific drugs used.

## Is a clinical trial an option for me?

Clinical trials are available for many stages and types of colon cancer and may offer access to new therapies. Your eligibility depends on your cancer’s stage, type, and molecular features. Ask your care team about current trials.

## What is the chance my colon cancer could come back?

The risk of recurrence depends on the stage at diagnosis, tumor features, and response to treatment. Early-stage cancers have a lower risk of recurrence, while advanced-stage cancers have a higher risk. Regular follow-up is essential.

## If you can’t cure cancer, can you keep it from spreading?

If cure is not possible, treatments aim to control the cancer, slow its growth, and relieve symptoms. Options may include chemotherapy, targeted therapy, immunotherapy, and palliative care.

## If you can’t stop the cancer, should I have palliative care?

Yes, palliative care is recommended to help manage symptoms, improve quality of life, and support you and your family at any stage of colon cancer—not just at the end of life.

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## **Genomic Data of Colon Cancer**

## Key Genetic Pathways and Mutations

Colon cancer develops through several well-defined genetic pathways, each involving specific gene alterations:

## 1. Chromosomal Instability (CIN) Pathway

* Most common pathway in colorectal cancer.
* Characterized by widespread chromosomal changes (aneuploidy, loss of heterozygosity).
* Key genes involved:
  + APC (5q): Frequently the first gene mutated; loss leads to uncontrolled cell growth and polyp formation.
  + TP53 (17p): Mutated in about 50% of colorectal cancers; a late event in progression from adenoma to carcinoma.
  + KRAS: Activating mutations in this oncogene are common and drive tumor growth.
  + SMAD4, DCC, PIK3CA, FBXW7: Additional tumor suppressors and oncogenes often altered.

## 2. Microsatellite Instability (MSI) Pathway

* Caused by defects in DNA mismatch repair (MMR) genes.
* Key genes:
  + MLH1, MSH2, MSH6, PMS2, EPCAM: Mutations in these genes lead to Lynch syndrome (hereditary non-polyposis colorectal cancer), the most common hereditary form of colon cancer.
* MSI-high tumors have a better prognosis and may respond differently to immunotherapy.

## 3. CpG Island Methylator Phenotype (CIMP) Pathway

* Involves widespread DNA methylation, silencing tumor suppressor genes.
* Often overlaps with MSI and BRAF mutations.

## Other Important Genes and Syndromes

* BRAF: Mutated in about 7% of cases, often mutually exclusive with KRAS mutations.
* NRAS: Less common, found in about 6% of cases.
* PTEN, MET, ERBB2, PIK3CA: Additional genes implicated in some tumors.
* Inherited syndromes:
  + Familial Adenomatous Polyposis (FAP): Caused by inherited APC mutations.
  + Peutz-Jeghers syndrome: Caused by STK11 mutations.
  + MUTYH-associated polyposis (MAP): Caused by MUTYH mutations.
  + PTEN hamartoma tumor syndrome: Associated with PTEN mutations, which can also increase colon cancer risk.

## Frequency of Key Mutations (Recent Sequencing Data)

* TP53: ~52%
* KRAS: ~47%
* APC: ~39%
* Other recurrent mutations: KDR, PIK3CA, SMAD4, BRAF, FBXW7, NRAS, MET, PTEN.

## Clinical Implications

* Genetic testing is recommended for patients with a strong family history or features suggestive of hereditary colon cancer.
* Molecular profiling (including KRAS, NRAS, BRAF, and MMR/MSI status) guides therapy, especially for advanced disease (e.g., anti-EGFR therapy only works in tumors without KRAS/NRAS mutations).

**REFERENCES**

[Colon Cancer: Symptoms, Stages & Treatment](https://my.clevelandclinic.org/health/diseases/14501-colorectal-colon-cancer#outlook-prognosis)

<https://emedicine.medscape.com/article/277496-guidelines>

[Colon cancer - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/colon-cancer/diagnosis-treatment/drc-20353674)

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# **COLORECTAL CANCER**

**DEFINITION AND DESCRIPTION**

Colorectal cancer starts in the colon or the rectum. These cancers can also be called colon cancer or rectal cancer, depending on where they start. Colon cancer and rectal cancer are often grouped together because they have many features in common.

## **How does colorectal cancer start?**

### **Polyps in the colon or rectum**

Most colorectal cancers start as a growth on the inner lining of the colon or rectum. These growths are called polyps.

Polyps are quite common, especially as you get older. Most polyps are benign, or noncancerous. Some types of polyps can change into cancer over time (usually over many years). The chance of a polyp turning into cancer depends on the type of polyp it is. There are different types of polyps.

* Adenomatous polyps (adenomas): These polyps sometimes change into cancer. Because of this, adenomas are called a precancerous condition. The 3 types of adenomas are tubular, villous, and tubulovillous. Tubular adenomas are the most common type of adenomatous polyps. Villous adenomas are the least common type of adenomatous polyps, but are more likely to change into cancer.
* Hyperplastic polyps and inflammatory polyps: These polyps are more common, but in general they are not precancerous. Some people with large (more than 1cm) hyperplastic polyps might need colorectal cancer screening with colonoscopy more often.
* Sessile serrated polyps (SSP) and traditional serrated adenomas (TSA): These polyps are often treated like adenomas because they have a higher risk of changing into cancer.

Other factors that can make a polyp more likely to contain cancer or increase someone’s risk of developing colorectal cancer include:

* Size: If a polyp larger than 1 cm
* Number: If more than 3 polyps are found
* Histology: If dysplasiais seen in the polyp. Dysplasia means that the cells look abnormal, but they haven’t yet become cancerous.

## **How colorectal cancer spreads**

If cancer forms in a polyp, it can grow into the wall of the colon or rectum over time. The wall of the colon and rectum is made up of many layers. Colorectal cancer starts in the innermost layer (the mucosa) and can grow outward through some or all of the other layers (see picture below).

When cancer cells are in the wall, they can then grow into blood vessels or lymph vessels (tiny channels that carry away waste and fluid). From there, they can travel to nearby lymph nodes or to distant parts of the body.

The stage (extent of spread) of a colorectal cancer depends on how deeply it grows into the wall and if it has spread outside the colon or rectum.

# **Colorectal Cancer Stages**

After someone is diagnosed with colorectal cancer, doctors will try to figure out if it has spread, and if so, how far. This process is called staging. The stage of a cancer describes how much cancer is in the body. It helps determine how serious the cancer is and how best to treat it. Doctors also use a cancer's stage when talking about survival statistics.

The earliest stage of colorectal cancers is called stage 0 (a very early cancer), and then range from stages I (1) through IV (4). As a rule, the lower the number, the less the cancer has spread. A higher number, such as stage IV, means cancer has spread more. And within a stage, an earlier letter means a lower stage. Although each person’s cancer experience is unique, cancers with similar stages tend to have a similar outlook and are often treated in much the same way.

The staging system most often used for colorectal cancer is the American Joint Committee on Cancer (AJCC) TNM system, which is based on 3 key pieces of information:

* The extent (size) of the tumor (T): How far has the cancer grown into the wall of the colon or rectum? These layers, from the inner to the outer, include:
  + The inner lining (mucosa), which is the layer in which nearly all colorectal cancers start. This includes a thin muscle layer (muscularis mucosa).
  + The fibrous tissue beneath this muscle layer (submucosa)
  + A thick muscle layer (muscularis propria)
  + The thin, outermost layers of connective tissue (subserosa and serosa) that cover most of the colon but not the rectum
* The spread to nearby lymph nodes (N): Has the cancer spread to nearby lymph nodes?
* The spread (metastasis) to distant sites (M): Has the cancer spread to distant lymph nodes or distant organs such as the liver or lungs?

The system described below is the most recent AJCC system effective January 2018. It uses the pathologic stage(also called thesurgical stage), which is determined by examining tissue removed during an operation. This is also known as surgical staging. This is likely to be more accurate than clinical staging, which takes into account the results of a physical exam, biopsies, and imaging tests, done *before* surgery.

Numbers or letters after T, N, and M provide more details about each of these factors. Higher numbers mean the cancer is more advanced. Once a person’s T, N, and M categories have been determined, this information is combined in a process called stage grouping to assign an overall stage. Cancer staging can be complex, so ask your doctor to explain it to you in a way you understand.

| **AJCC Stage** | **Stage grouping** | **Stage description\*** |
| --- | --- | --- |
| 0 | Tis  N0  M0 | The cancer is in its earliest stage. This stage is also known as carcinoma in situ or intramucosal carcinoma (Tis). It has not grown beyond the inner layer (muscularis mucosa) of the colon or rectum. |
| I | T1 or T2  N0  M0 | The cancer has grown through the muscularis mucosa into the submucosa (T1), and it may also have grown into the muscularis propria (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). |
| IIA | T3  N0  M0 | The cancer has grown into the outermost layers of the colon or rectum but has not gone through them (T3). It has not reached nearby organs. It has not spread to nearby lymph nodes (N0) or to distant sites (M0). |
| IIB | T4a  N0  M0 | The cancer has grown through the wall of the colon or rectum but has not grown into other nearby tissues or organs (T4a). It has not yet spread to nearby lymph nodes (N0) or to distant sites (M0). |
| IIC | T4b  N0  M0 | The cancer has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organs (T4b). It has not yet spread to nearby lymph nodes (N0) or to distant sites (M0). |
| IIIA | T1 or T2  N1/N1c  M0 | The cancer has grown through the muscularis mucosa into the submucosa (T1), and it may also have grown into the muscularis propria (T2). It has spread to 1 to 3 nearby lymph nodes (N1) or into areas of fat near the lymph nodes but not the nodes themselves (N1c). It has not spread to distant sites (M0). |
| OR | |
| T1  N2a  M0 | The cancer has grown through the muscularis mucosa into the submucosa (T1). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites (M0). |
| IIIB | T3 or T4a  N1/N1c  M0 | The cancer has grown into the outermost layers of the colon or rectum (T3) or through the wall of the colon or rectum (including the visceral peritoneum) (T4a) but has not reached nearby organs. It has spread to 1 to 3 nearby lymph nodes (N1a or N1b) or into areas of fat near the lymph nodes but not the nodes themselves (N1c). It has not spread to distant sites (M0). |
| OR | |
| T2 or T3  N2a  M0 | The cancer has grown into the muscularis propria (T2) or into the outermost layers of the colon or rectum (T3). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites (M0). |
| OR | |
| T1 or T2  N2b  M0 | The cancer has grown through the muscularis mucosa into the submucosa (T1), and it might also have grown into the muscularis propria (T2). It has spread to 7 or more nearby lymph nodes (N2b). It has not spread to distant sites (M0). |
| IIIC | T4a  N2a  M0 | The cancer has grown through the wall of the colon or rectum (including the visceral peritoneum) but has not reached nearby organs (T4a). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites (M0). |
| OR | |
| T3 or T4a  N2b  M0 | The cancer has grown into the outermost layers of the colon or rectum (T3) or through the wall of the colon or rectum (including the visceral peritoneum) (T4a) but has not reached nearby organs. It has spread to 7 or more nearby lymph nodes (N2b). It has not spread to distant sites (M0). |
| OR | |
| T4b  N1 or N2  M0 | The cancer has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organs (T4b). It has spread to at least 1 nearby lymph node or into areas of fat near the lymph nodes (N1 or N2). It has not spread to distant sites (M0). |
| IVA | Any T  Any N  M1a | The cancer may or may not have grown through the wall of the colon or rectum (Any T). It might or might not have spread to nearby lymph nodes. (Any N). It has spread to 1 distant organ (such as the liver or lung) or distant set of lymph nodes, but not to distant parts of the peritoneum (the lining of the abdominal cavity) (M1a). |
| IVB | Any T  Any N  M1b | The cancer might or might not have grown through the wall of the colon or rectum (Any T). It might or might not have spread to nearby lymph nodes (Any N). It has spread to more than 1 distant organ (such as the liver or lung) or distant set of lymph nodes, but not to distant parts of the peritoneum (the lining of the abdominal cavity) (M1b). |
| IVC | Any T  Any N  M1c | The cancer might or might not have grown through the wall of the colon or rectum (Any T). It might or might not have spread to nearby lymph nodes (Any N). It has spread to distant parts of the peritoneum (the lining of the abdominal cavity), and may or may not have spread to distant organs or lymph nodes (M1c). |

\* The following additional categories are not listed in the table above:

* TX: Main tumor cannot be assessed due to lack of information.
* T0: No evidence of a primary tumor.
* NX: Regional lymph nodes cannot be assessed due to lack of information.

## **Risk factors you can change**

Many lifestyle-related factors have been linked to colorectal cancer. In fact, more than half of all colorectal cancers are linked to risk factors that can be changed.

### **Excess body weight**

If you have excess body weight (overweight or obesity), your risk of developing and dying from colorectal cancer is higher. Excess weight raises the risk of colorectal cancer in people, but the link seems to be stronger in men. Getting to and staying at a healthy weight may help lower your risk.

### **Diabetes mellitus, Type 2**

People with type 2 diabetes mellitus are more likely than people who don’t to develop colorectal cancer. Researchers suspect that this higher risk may be due to high levels of insulin in people with diabetes mellitus. Both type 2 diabetes and colorectal cancer share some of the same risk factors (such as excess body weight and physical inactivity). But even after taking these factors into account, people with type 2 diabetes still have an increased risk. They also tend to have a less favorable prognosis (outlook) after diagnosis.

### **Certain types of diets**

A long-term diet that's high in red meats (such as beef, pork, lamb, or liver) and processed meats (like hot dogs and some lunch meats) raises your colorectal cancer risk.

Cooking meats at very high temperatures (frying, broiling, or grilling) creates chemicals that might raise your cancer risk.

Having a low blood level of vitamin D may also increase your risk.

Following a healthy eating pattern that includes plenty of fruits, vegetables, and whole grains, and that limits or avoids red and processed meats and sugary drinks probably lowers risk.

### **Smoking**

People who have smoked tobacco for a long time are more likely to develop and die from colorectal cancer than people who don't smoke. Smoking tobacco also increases the risk for people to develop colon polyps. Smoking is a well-known cause of lung cancer, but it's linked to a lot of other cancers, too. If you smoke and want to know more about quitting,

**Alcohol use**

Colorectal cancer has been linked to moderate to heavy alcohol use. Even light-to-moderate alcohol intake has been associated with some risk. It is best not to drink alcohol. If people do drink alcohol, they should have no more than 2 drinks a day for men and 1 drink a day for women. This could have many health benefits, including a lower risk of many kinds of cancer.

## **Colorectal cancer risk factors you cannot change**

### **Your age**

Your risk of colorectal cancer goes up as you age. Younger adults can get it, but it’s much more common after age 50. Colorectal cancer is rising among people who are younger than age 50, and the reason for this remains unclear.

### **Your racial and ethnic background**

American Indian and Alaska Native people have the highest rates of colorectal cancer in the United States, followed by African American men and women.

Jews of Eastern European descent (Ashkenazi Jews) have one of the highest colorectal cancer risks of any ethnic group in the world.

### **Your sex at birth**

Men who have colorectal cancer are more likely to die from it than women. The reasons are not fully clear. Women who have colorectal cancer are more likely to have right-sided colon cancer, particularly if they are no longer menstruating (postmenopausal).

### **Cholecystectomy**

People who have had their gallbladder removed (cholecystectomy) have been found to have a mildly higher risk for right-sided colon cancer. It’s not fully understood why this is. Research is ongoing.

### **A personal history of colorectal polyps or colorectal cancer**

If you have a history of adenomatous polyps (adenomas), you are at increased risk of developing colorectal cancer. This is especially true if the polyps are large, if there are many of them, or if any of them show dysplasia.

If you’ve had colorectal cancer, even though it was completely removed, you are more likely to develop new cancers in other parts of the colon and rectum. The chances of this happening are greater if you had your first colorectal cancer when you were younger.

### **A personal history of inflammatory bowel disease**

If you have inflammatory bowel disease (IBD), including either ulcerative colitis or Crohn’s disease, your risk of colorectal cancer is increased.

IBD is a condition in which the colon is inflamed over a long period of time. People who have had IBD for many years, especially if untreated, often develop dysplasia. Dysplasia is a term used to describe cells in the lining of the colon or rectum that look abnormal, but are not cancer cells. They can change into cancer over time.

If you have IBD, you may need to start getting screened for colorectal cancer when you are younger and be screened more often.

Inflammatory bowel disease is different from irritable bowel syndrome (IBS), which does not appear to increase your risk for colorectal cancer.

### **A personal history of radiation to the abdomen or pelvis area**

If you survived cancer in the past and as part of your treatment, received radiation to the area where your colon is (abdomen and pelvis area), your risk of colorectal cancer is increased. If you have received radiation to the abdomen or pelvis, especially as a child, you may need to start getting screened for colorectal cancer when you are younger and be screened more often.

Several studies suggest that men who had radiation therapy to treat prostate cancer might have a higher risk of rectal cancer because the rectum receives some radiation during treatment. Most of these studies are based on men treated in the 1980s and 1990s, when radiation treatments were less precise than they are today. The effect of more modern radiation methods on rectal cancer risk is not clear, but research continues to be done in this area.

### **A family history of colorectal cancer or adenomatous polyps**

Most colorectal cancers are found in people without a family history of colorectal cancer. Still, as many as 1 in 3 people who develop colorectal cancer have other family members who have had it.

People with a history of colorectal cancer in a first-degree relative (parent, sibling, or child) are at increased risk. The risk is even higher if that relative was diagnosed with cancer when they were younger than age 50, or if more than one first-degree relative is affected.

The reasons for the increased risk are not clear in all cases. Cancers can “run in the family” because of inherited genes, shared environmental factors, or some combination of these.

Having family members who have had adenomatous polyps is also linked to a higher risk of colon cancer. (Adenomatous polyps are the kind of polyps that can become cancerous.)

If you have a family history of adenomatous polyps or colorectal cancer, talk with your doctor about the possible need to start screening at a younger age. If you've had adenomatous polyps or colorectal cancer, it’s important to tell your close relatives so that they can pass along that information to their doctors and start screening at the right age.

### **Having an inherited syndrome**

About 5% of people who develop colorectal cancer have inherited gene changes (mutations) that cause family cancer syndromes and can lead to them getting the disease.

The most common inherited syndromes linked with colorectal cancers are Lynch syndrome (hereditary non-polyposis colorectal cancer, or HNPCC) and familial adenomatous polyposis (FAP), but other rarer syndromes can increase colorectal cancer risk, too.

#### **Lynch syndrome (hereditary non-polyposis colon cancer or HNPCC)**

Lynch syndrome is the most common hereditary colorectal cancer syndrome. It accounts for about 2% to 4% of all colorectal cancers. In most cases, this disorder is caused by an inherited defect in either the *MLH1*, *MSH2,MSH6, PMS2, or EPCAM* gene, but changes in other genes can also cause Lynch syndrome. These genes, called DNA mismatch repair (MMR) genes, normally help repair DNA that has been damaged.

The cancers linked to this syndrome tend to develop when people are relatively young and tend to develop right-sided colon cancer. People with Lynch syndrome can have polyps, but they tend to have only a few. The lifetime risk of colorectal cancer in people with this condition may be as high as 50%, but this depends on which gene is affected.

Women with this condition also have a very high risk of developing cancer of the endometrium (lining of the uterus). Other cancers linked with Lynch syndrome include cancer of the ovary, stomach, small intestine, pancreas, kidney, prostate, breast, ureters (tubes that carry urine from the kidneys to the bladder), and bile duct. People with Turcot syndrome (a rare inherited condition) who have a defect in one of the Lynch syndrome genes are at a higher risk of colorectal cancer as well as a specific type of brain cancer called glioblastoma.

#### **Familial adenomatous polyposis (FAP)**

FAP is caused by changes (mutations) in the *APC* gene that a person inherits from their parents. About 1% of all colorectal cancers are caused by FAP.

In the most common type of FAP, hundreds or thousands of polyps develop in a person’s colon and rectum, often starting at ages 10 to 12. Cancer usually develops in 1 or more of these polyps as early as age 20. By age 40, almost all people with FAP will have colon cancer if their colon hasn’t been removed to prevent it. People with FAP also have an increased risk for cancers of the stomach, small intestines, pancreas, liver, and some other organs.

There are 3 sub-types of FAP:

* In attenuated FAP or AFAP, patients have fewer polyps (less than 100), and colorectal cancer tends to occur at a later age (40s and 50s).
* Gardner syndrome is a type of FAP that also causes noncancerous tumors of the skin, soft tissue, and bones.
* In Turcot syndrome, people who have *APC* gene mutation are at a high risk of having many adenomatous polyps and colorectal cancer, but also a specific type of brain cancer called medulloblastoma.

#### **Rare inherited conditions linked to colorectal cancer**

* Peutz-Jeghers syndrome (PJS): People with this inherited condition tend to have freckles around the mouth (and sometimes on their hands and feet) and a special type of polyp called hamartomas in their digestive tract. These people are at a much higher risk for colorectal cancer, as well as other cancers, such as cancers of the breast, ovary, and pancreas. They usually are diagnosed at a younger than usual age. This syndrome is caused by mutations in the *STK11 (LKB1)* gene*.*
* MUTYH-associated polyposis (MAP): People with this syndrome develop many colon polyps. These tend to become cancer if not watched closely with routine colonoscopies. These people also have an increased risk of other cancers of the GI (gastrointestinal) tract, breast, ovary, bladder, and thyroid. This syndrome is caused by mutations in the *MUTYH* gene (which is involved in “proofreading” the DNA and fixing any mistakes) and often leads to cancer at a younger age.
* Cystic fibrosis (CF): CF is an inherited condition in which the cells in some body organs make mucus that is thicker and stickier than normal. This can lead to health problems, especially in the lungs and pancreas. As better medical care has helped people with CF live longer, it’s become clear that people with CF are also at increased risk for colorectal cancer, which usually occurs at a much earlier age than in people without the condition. The risk for colorectal cancer is even higher in people who have had an organ transplant, such as a lung transplant. CF is caused by mutations in the *CFTR* gene.

Since many of these syndromes are linked to colorectal cancer at a young age and other types of cancer, identifying families with these inherited syndromes is important. It lets doctors recommend specific steps such as screening and other preventive measures when the person is younger. Information on risk assessment, and genetic counseling and testing for many of these syndromes can be found in Genetic Testing, Screening, and Prevention for People with a Strong Family History of Colorectal Cancer.

**CAUSES**

## **Gene changes that may lead to colorectal cancer**

Cancer is caused by changes in the DNA inside our cells. DNA is the substance in our cells that makes up our genes, which control how our cells function. We usually look like our parents because they are the source of our DNA. But DNA affects more than just how we look.

Some genes help control when our cells grow, divide into new cells, and die:

* Certain genes that help cells grow, divide, and stay alive are called oncogenes.
* Genes that help keep cell division under control or instruct cells to die at the right time are called tumor suppressor genes.

Cancers can be caused by DNA mutations (changes) that turn on oncogenes or turn off tumor suppressor genes. This leads to cells growing out of control. Changes in many different genes are usually needed to cause colorectal cancer.

## **Inherited (germline) gene ﻿mutations**

Some DNA mutations can be passed on in families and are found in all of a person’s cells. These are called inherited mutations. A very small portion of colorectal cancers are caused by inherited gene mutations. Many of these DNA changes and their effects on the growth of cells are now known. For example:

* Familial adenomatous polyposis (FAP), attenuated FAP (AFAP), and Gardner syndrome are caused by inherited changes in the *APC* gene. The *APC* gene is a tumor suppressor gene; it normally helps keep cell growth in check. In people with inherited changes in the *APC* gene, this “brake” on cell growth is turned off, causing hundreds of polyps to form in the colon. Over time, cancer will nearly always develop in one or more of these polyps.
* Lynch syndrome (hereditary non-polyposis colon cancer, or HNPCC) is caused by changes in genes that normally help a cell repair damaged DNA. A mutation in one of the DNA repair genes like *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* can allow DNA errors to go unfixed. These errors will sometimes affect growth-regulating genes, which may lead to the development of cancer.
* Peutz-Jeghers syndrome is caused by inherited changes in the *STK11 (LKB1)* gene, a tumor suppressor gene.
* MUTYH-associated polyposis (MAP) is caused by mutations in the *MUTYH* gene, which impacts how the cell “proofreads” or checks the DNA and fixes errors when cells divide.
* Cystic fibrosis (CF) is caused by inherited mutations in the *CFTR* gene. Exactly how changes in this gene increase colorectal cancer risk isn’t yet clear.

Special genetic tests can find gene mutations linked to these inherited conditions. If you have a family history of colorectal polyps or cancer or other symptoms linked to one of these conditions, you may want to ask your doctor about genetic counseling and genetic testing.

## **Acquired (somatic) gene mutations**

Most gene mutations that lead to cancer are acquiredorsomatic mutations. They happen during a person’s lifetime and are not passed on to their children. These DNA changes only affect cells that come from the original mutated cell.

In most cases of colorectal cancer, the DNA mutations that lead to cancer are acquired during a person’s life rather than having been inherited. Certain risk factors probably play a role in causing these acquired mutations, but so far it’s not known what causes most of them.

There doesn’t seem to be a single genetic pathway to colorectal cancer that’s the same in all cases. In many cases, the first mutation occurs in the *APC* gene. This leads to an increased growth of colorectal cells because of the loss of this “brake” on cell growth. Further mutations may then occur in other genes, which can lead the cells to grow and spread uncontrollably. Other genes that aren’t known yet are probably involved as well.

## 

## **Types of colorectal cancer screening tests**

There are 3 main types of colorectal cancer screening tests :

* Stool-based tests: These tests check the stool (feces) for signs of colon or rectal cancer, such as small amounts of blood. These tests are not invasive and are easier to have done than visual exams, but they need to be done more often.
* Visual exams: These tests look inside the colon and rectum for any abnormal areas. They are done either with a scope (a tube-like instrument with a light and tiny video camera on the end) that is placed into the rectum, or with special imaging tests.
* Blood-based tests: These tests check a person's blood for signs of colorectal cancer.

These tests each have different benefits, limits, and harms (see the table below), and some of them might be better choices for you than others.

If you choose to be screened with a test other than colonoscopy, any abnormal test result should be followed up with a timely colonoscopy.

Some of these tests (especially colonoscopy) might also be used if you have symptoms that might be caused by other digestive diseases.

## **Stool-based tests**

These tests look at the stool (feces) for possible signs of colorectal cancer or polyps, such as small amounts of blood or changes in the DNA or RNA from cells in the stool.

These tests can be done at home, and many people find they are more convenient and easier to have than visual tests like a colonoscopy. Stool-based tests, however, need to be done more often compared with visual exams.

If the result from a stool-based test is abnormal, you will still need a colonoscopy to see if you have colorectal cancer.

All stool-based tests look for occult (hidden) blood in the stool, and some look for other possible signs of cancer as well. The idea behind this is that blood vessels in larger colorectal polyps or in cancers are often fragile and easily damaged when stool passes through. The damaged vessels usually bleed into the colon or rectum, but only rarely is there enough blood for it to be seen by the naked eye in the stool.

### **Fecal immunochemical test (FIT)**

The fecal immunochemical test (FIT) checks for hidden blood in the stool from the lower intestines. If you choose this test, it should be done every year, in the privacy of your home. Sometimes this test is called iFOBT or immunochemical fecal occult blood test.

Unlike the guaiac-based fecal occult blood test (gFOBT, see below), the FIT test does not have any drug or dietary restrictions because vitamins and foods do not affect the test results. Collecting the samples may also be easier. This test is also less likely to react to bleeding from the upper parts of the digestive tract, such as the stomach.

Collecting the samples: Your health care provider will give you the supplies you need for testing. Have all your supplies ready and in one place. Supplies typically include a test kit, test cards or tubes, long brushes or other collecting devices, waste bags, and a mailing envelope. The kit will give you detailed instructions on how to collect the samples. Be sure to follow the instructions that come with your kit. If you have any questions about how to use your kit, contact your health care provider’s office or clinic. Once you have collected the samples, return them (generally within 24 hours) as instructed.

If the test result is positive (that is, if hidden blood is found), a colonoscopy will be needed to investigate further. Although blood in the stool can be from cancer or polyps, it can also be from other causes, such as ulcers, hemorrhoids, or other conditions.

### **Guaiac-based fecal occult blood test (gFOBT)**

The guaiac-based fecal occult blood test (gFOBT) finds occult (hidden) blood in the stool through a chemical reaction. It works differently from the fecal immunochemical test (FIT). Unlike the FIT, the gFOBT can’t tell if the blood is from the colon or from other parts of the digestive tract (such as the stomach).

If you choose this test, it should be done every year, in the privacy of your home. It checks more than one stool sample. The American Cancer Society recommends that only the highly sensitive versions of this test be used.

An FOBT done during a digital rectal exam in the doctor’s office is not enough for proper screening, because it is more likely to miss some colorectal cancers.

Before the test: Some foods or drugs can affect the results of this test, so you may be instructed to avoid the following before this test:

* Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen (Advil), naproxen (Aleve), or aspirin, for 7 days before testing. (They can cause bleeding, which can lead to a false-positive result.) Note: You should try to avoid taking NSAIDs for minor aches prior to the test. But if you take these medicines daily for heart problems or other conditions, don’t stop them for this test without talking to your health care provider first.
* Vitamin C (more than 250 mg a day) from either supplements or citrus fruits and juices for 3 to 7 days before testing. (This can affect the chemicals in the test and make the result negative, even if blood is present.)
* Red meats (beef, lamb, or liver) for 3 days before testing. (Components of blood in the meat may cause a positive test result.)

Some people who are given the test never do it or don’t return it because they worry that something they ate may affect the test. Even if you are concerned that something you ate may alter the test result, the most important thing is to get the test done.

Collecting the samples: You will get a kit with instructions from your health care provider’s office or clinic. The kit will explain how to take stool samples at home (usually samples from 3 separate bowel movements are smeared onto small paper cards). The kit is then returned to the doctor’s office or medical lab for testing.

To do this test, have all your supplies ready and in one place. Supplies typically include a test kit, test cards, either a brush or wooden applicator, and a mailing envelope. The kit will give you detailed instructions on how to collect the stool samples. Be sure to follow the instructions that come with your kit. If you have any questions about how to use your kit, contact your health care provider’s office or clinic. Once you have collected the samples, return them as instructed in the kit.

If the test result is positive (if hidden blood is found), a colonoscopy will be needed to find the reason for the bleeding.

### **Multitarget stool DNA or RNA tests**

Multitarget stool DNA or RNA tests with fecal immunochemical testing (FIT) look for certain abnormal sections of DNA or RNA from cancer or polyp cells, as well as for occult (hidden) blood. Colorectal cancer or polyp cells often have DNA or RNA mutations (changes). Cells with these mutations often get into the stool, where tests may be able to find them.

* Cologuard tests for DNA changes and blood in the stool.
* ColoSense tests for RNA changes and blood in the stool.\*

\*ColoSense is approved by the US Food and Drug Administration (FDA), but it has not yet been evaluated for inclusion in colorectal cancer screening guidelines by the American Cancer Society or the US Preventive Services Task Force (USPSTF). Because it’s not included in the current USPSTF recommendations, insurance coverage may not be available.

If you choose one of these tests, it should be done every 3 years. They are done in the privacy of your own home. They test a full bowel movement. There are no drug or dietary restrictions before taking the test.

Collecting the samples: You’ll get a kit in the mail to use to collect your entire stool sample at home. The kit will have a sample container, a bracket for holding the container in the toilet, a bottle of liquid preservative, a tube, labels, a FIT test (see above), and a shipping box. The kit has detailed instructions on how to collect the sample. Be sure to follow the instructions that come with your kit. If you have any questions about how to use your kit, contact your doctor’s office or clinic. Once you have collected the sample, return it as instructed in the kit.

If the test result is positive (if it finds DNA changes, RNA changes, or blood), a colonoscopy will need to be done.

For information on the differences between these tests and other colorectal cancer screening tests, see the table below.

## **Visual exams**

These tests look at the inside of the colon and rectum for any abnormal areas that might be cancer or polyps.

### **Colonoscopy**

For this test, the doctor looks at the entire length of the colon and rectum with a colonoscope, a flexible tube with a light and small video camera on the end. It’s put in through the anus and into the rectum and colon. Special instruments can be passed through the colonoscope to biopsy (take samples) or remove any suspicious-looking areas such as polyps, if needed.

### **CT colonography (virtual colonoscopy)**

This test is an advanced type of computed tomography (CT) scan of the colon and rectum that can show abnormal areas, like polyps or cancer. Special computer programs use both x-rays and a CT scan to make 3-dimensional pictures of the inside of the colon and rectum. It does not require sedation (medicine to sleep) or a scope to be put into the rectum or colon. A small catheter is placed into your rectum to fill your colon with air or carbon dioxide. This allows for clearer CT pictures.

This test may be useful for some people who can’t have or don’t want to have an invasive test such as a colonoscopy. It can be done fairly quickly, but it requires the same type of bowel prep as a colonoscopy.

If polyps or other suspicious areas are seen on this test, a colonoscopy will still be needed to remove them or to explore the area fully.

Before the test: It’s important that the colon and rectum are emptied before this test to get the best images. You’ll probably be told to follow the same instructions to clean out the intestines as someone getting a colonoscopy.

During the test: This test is done in a special room with a CT scanner. It takes about 15 minutes. You’ll be asked to lie on a narrow table that’s part of the CT scanner, and will have a small, flexible tube put into your rectum. Air is pumped through the tube into the colon and rectum to expand them to provide better pictures. The table then slides into the CT scanner, and you’ll be asked to hold your breath for a few seconds while the scan is done. You’ll likely have 2 scans: 1 while you’re lying on your back and 1 while you’re on your stomach or side.

**Possible side effects and complications:**

There are usually few side effects after this test. You may feel bloated or have cramps because of the air in the colon and rectum, but this should go away once the air passes from the body. There’s a very small risk that inflating the colon with air could injure or puncture it, but this risk is thought to be much less than with colonoscopy. Like other types of CT scans, this test also exposes you to a small amount of radiation.

### **Sigmoidoscopy**

A sigmoidoscopy is like a colonoscopy except it doesn’t examine the entire colon. A sigmoidoscope, a flexible, lighted tube with a small video camera on the end, is inserted in through the anus, into the rectum, and then moved into the lower part of the colon. The sigmoidoscope is only about 2 feet (60 cm) long, so the doctor can only see the entire rectum and less than half of the colon. Images from the scope are seen on a video screen so the doctor can find and possibly remove any abnormal areas.

This test is not widely used as a screening tool for colorectal cancer in the United States. This is mainly because a sigmoidoscopy looks only at the lower portion (left side) of your colon, while at least 4 out of 10 colorectal cancers start in the upper portion (right side) of the colon.

Before the test: The colon and rectum should be emptied before this test to get the best pictures (known as bowel prep). You’ll probably need to take medicines such as enemas to clean out the intestines before the test, although this is likely to be less intense than the bowel prep needed before a colonoscopy.

During the test: A sigmoidoscopy usually takes about 10 to 20 minutes. Most people don’t need to be sedated for this test, but this might be an option you can discuss with your doctor. Sedation may make the test less uncomfortable, but you’ll need some time to recover from it, and you’ll need someone with you to take you home after the test.

You’ll probably be asked to lie on a table on your left side with your knees pulled up near your chest. Before the test, your doctor may put a gloved, lubricated finger into your rectum to examine it. The sigmoidoscope is first lubricated to make it easier to put into the rectum. Air is then pumped into the colon and rectum through the sigmoidoscope so the doctor can see the inner lining better. This might be uncomfortable, but it should not be painful. Be sure to let your doctor know if you feel pain during the procedure.

If you are not sedated during the procedure, you might feel pressure and slight cramping in your lower belly. To ease discomfort and the urge to have a bowel movement, it may help to breathe deeply and slowly through your mouth. You’ll feel better after the test once the air leaves your bowels.

If any polyps are found during the test, the doctor may remove them with a small instrument passed through the scope. The polyps will be looked at in the lab. If a precancerous polyp (an adenoma) or colorectal cancer is found, you’ll need to have a colonoscopy later to look for polyps or cancer in the rest of the colon.

Possible complications and side effects: You might see a small amount of blood in your bowel movements for a day or 2 after the test. More serious bleeding and puncture of the colon or rectum are possible, but they are not common.

## **Blood-based tests**

There are 2 FDA-approved, blood-based tests for colorectal screening in people who are at average risk:

* Shield
* ColoHealth (previously Epi proColon)

These tests look for possible signs of colorectal cancer or precancerous polyps in a person's blood, although they are more accurate at detecting colorectal cancer than pre-cancerous polyps.

These tests are done in a clinic, where a sample of your blood will be collected and sent to a lab. In the lab, your blood will be tested for certain DNA changes that could suggest the presence of cancer or pre-cancer cells. Medical insurance coverage may be different for each test.

Although these tests are FDA-approved, they have not been reviewed by the American Cancer Society, so they are not included as part of the ACS Guideline for Colorectal Cancer Screening at this time. They also have not been reviewed by the USPSTF, which means they might not be covered by private insurance without out-of-pocket costs. However, Medicare Part B covers the Shield blood test for colorectal cancer screening without out-of-pocket costs.

For a comparison of the different colorectal cancer screening tests, see the table below.

## **What are some of the benefits and limits of colorectal cancer screening tests?**

| **Test** | **Benefits** | **Limits** |
| --- | --- | --- |
| Blood-based test | No direct risk to the colon  No bowel prep  No pre-test diet or medication changes needed | Can miss many polyps and some cancers  Will need to have blood drawn in clinic  Medical insurance coverage may vary depending on which blood test is done  Colonoscopy will be needed if results are abnormal |
| Fecal immunochemical test (FIT) | No direct risk to the colon  No bowel prep  No pre-test diet or medication changes needed  Sampling done at home  Inexpensive | Can miss many polyps and some cancers  Can have false-positive test results  Needs to be done every year  Colonoscopy will be needed if results are abnormal |
| Guaiac-based fecal occult blood test (gFOBT) | No direct risk to the colon  No bowel prep  Sampling done at home  Inexpensive | Can miss many polyps and some cancers  Can have false-positive test results  Pre-test changes in diet (and possibly medication) are needed  Needs to be done every year  Colonoscopy will be needed if results are abnormal |
| Stool DNA test | No direct risk to the colon  No bowel prep  No pre-test diet or medication changes needed  Sampling done at home | Can miss many polyps and some cancers  Can have false-positive test results  Should be done every 3 years  Colonoscopy will be needed if results are abnormal |
| Colonoscopy | Can usually look at the entire colon  Can biopsy and remove polyps  Done every 10 years  Can help find some other diseases | Full bowel prep needed  Costs more on a one-time basis than other forms of testing if a person is uninsured  Sedation is usually needed, in which case you will need someone to drive you home  You might miss a day of work  Small risk of bleeding, bowel tears, or infection |
| CT colonography (virtual colonoscopy) | Fairly quick and safe  Can usually see the entire colon  Done every 5 years  No sedation needed | Can miss small polyps  Full bowel prep needed  Some false-positive test results  Exposure to a small amount of radiation  Can’t remove polyps during testing  Colonoscopy will be needed if results are abnormal |
| Sigmoidoscopy | Fairly quick and safe  Sedation usually not used  Done every 5 years | Not widely used as a screening test  Bowel prep may still be requested  Looks at only about a third of the colon  Can miss small polyps and/or colorectal cancer  Can’t remove all polyps  May be some discomfort  Very small risk of bleeding, infection, or bowel tear  Colonoscopy will be needed if results are abnormal |

## **Common signs and symptoms of colorectal cancer**

* A change in bowel habits, such as diarrhea, constipation, or narrowing of the stool, that lasts for more than a few days
* A feeling that you need to have a bowel movement that’s not relieved by having one
* Rectal bleeding with bright red blood
* Blood in the stool, which might make the stool look dark brown or black
* Cramping or abdominal (belly) pain
* Weakness and fatigue
* Unintended weight loss

Colorectal cancers can often bleed into the digestive tract. Sometimes the blood can be seen in the stool or make it look darker, but often the stool looks normal. But over time, the blood loss can build up and can lead to low red blood cell counts (anemia). Sometimes the first sign of colorectal cancer is a blood test showing a low red blood cell count.

## **Signs of colorectal cancer that has spread**

Some people may have signs that the cancer has spread to the liver with a large liver felt on exam, jaundice (yellowing of the skin or whites of the eyes), or trouble breathing from cancer spread to the lungs.

## **Do colon polyps cause symptoms?**

Most people with polyps will not have any symptoms. However, some people may have symptoms from polyps, such as:

* Bleeding from the rectum
* Change in stool color, either red or black
* Change in bowel movement, either prolonged constipation or diarrhea
* Low red blood cell count due to low iron (iron deficiency anemia)
* Abdominal (belly) pain

These symptoms can also be due to other causes, such as foods, medicines, or other medical conditions. If these symptoms are present, you should discuss further with your doctor.

## **If you have signs or symptoms**

Many of these symptoms can be caused by conditions other than colorectal cancer, such as infection, hemorrhoids, or irritable bowel syndrome. Still, if you have any of these problems, it’s important to see your doctor right away so the cause can be found and treated, if needed.

**Diagnose and Stage Colorectal Cancer**

If you have symptoms that might be from colorectal cancer, or if a screening test shows something abnormal, your doctor will recommend one or more of the exams and tests below to find the cause.

## **Medical history and physical exam**

Your doctor will ask about your medical history to learn about possible risk factors, including your family history. You will also be asked if you’re having any symptoms and, if so, when they started and how long you’ve had them.

As part of a physical exam, your doctor will feel your abdomen for masses or enlarged organs, and also examine the rest of your body. You may also have a digital rectal exam (DRE). During this test, the doctor inserts a lubricated, gloved finger into your rectum to feel for any abnormal areas.

## **Tests to look for blood in your stool**

If you are seeing the doctor because of anemia or symptoms you are having (other than obvious bleeding from your rectum or blood in your stools), a stool test might be recommended to check for blood that isn’t visible to the naked eye (occult blood), which might be a sign of cancer. These types of tests – a fecal occult blood test (FOBT) or fecal immunochemical test (FIT) – are done at home and require you to collect 1 to 3 samples of stool from bowel movements.

(A stool blood test should not be the next test done if you’ve already had an abnormal screening test, in which case you should have a diagnostic colonoscopy, which is described below.)

## **Blood tests**

Your doctor might also order certain blood tests to help determine if you have colorectal cancer. These tests also can be used to help monitor your disease if you’ve been diagnosed with cancer.

Complete blood count (CBC): This test measures the different types of cells in your blood. It can show if you have anemia (too few red blood cells). Some people with colorectal cancer become anemic because the tumor has been bleeding for a long time.

Liver enzymes: You may also have a blood test to check your liver function, because colorectal cancer can spread to the liver.

Tumor markers: Colorectal cancer cells sometimes make substances called tumor markers that can be found in the blood. The most common tumor marker for colorectal cancer is the carcinoembryonic antigen (CEA).

Blood tests for this tumor marker can sometimes suggest someone might have colorectal cancer, but they can’t be used alone to screen for or diagnose cancer. This is because tumor marker levels can sometimes be normal in someone who has cancer and can be abnormal for reasons other than cancer.

Tumor marker tests are used most often along with other tests to monitor patients who have already been diagnosed with colorectal cancer and are receiving treatment. They may help show how well treatment is working or provide an early warning that a cancer has returned.

## **Diagnostic colonoscopy**

A diagnostic colonoscopy is just like a screening colonoscopy, but it’s done because a person is having symptoms, or because something abnormal was found on another type of screening test.

For this test, the doctor looks at the entire length of the colon and rectum with a colonoscope, a thin, flexible, lighted tube with a small video camera on the end. It is inserted through the anus and into the rectum and the colon. Special instruments can be passed through the colonoscope to biopsy or remove any suspicious-looking areas such as polyps, if needed.

Colonoscopy may be done in a hospital outpatient department or in a surgery clinic.

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## **Proctoscopy**

This test may be done if rectal cancer is suspected. For this test, the doctor looks inside the rectum with a proctoscope, a thin, rigid, lighted tube with a small video camera on the end. It’s put in through the anus. The doctor can look closely at the inside lining of the rectum through the scope. The tumor can be seen, measured, and its exact location can be determined. For instance, the doctor can see how close the tumor is to the sphincter muscles that control the passing of stool.

## **Biopsy**

If a suspected colorectal tumor is found during a screening or diagnostic test, it usually is biopsied. In a biopsy, the doctor removes a small piece of tissue with a special instrument passed through the scope. Less often, part of the colon may need to be surgically removed to make the diagnosis.

**Lab tests of biopsy samples**

Biopsy samples (from colonoscopy or surgery) are sent to the lab where they are looked at closely. If cancer is found, other lab tests may also be done on the biopsy samples to help better classify the cancer and guide specific treatment options. These are biomarker tests that look for genes, proteins, and other substances that can reveal important details about a person's cancer.

Molecular tests: If the cancer is advanced, the cancer cells will probably be tested for specific gene and protein changes that might help tell if targeted therapy drugs could be options for treatment. For example, the cancer cells are typically tested for changes (mutations) in the *KRAS, NRAS*, and *BRAF* genes, as well as other gene and protein changes.

* If the cancer cells are *not* found to have a mutation(s) in the *KRAS, NRAS*, or *BRAF* genes, then treatment with drugs that target EGFR proteins might be helpful.
* If the cancer cells are found to have a mutation in the *BRAF* gene, known as BRAF V600E, then treatment with drugs that target the BRAF and EGFR proteins might be helpful.
* Some colorectal cancers that don’t have mutations in the *KRAS, NRAS,* or *BRAF* genes might be tested to see if they make too much of the HER2 protein. For these cancers, treatment with drugs that target HER2 might be helpful.
* Colorectal cancers that don't have mutations in the *KRAS, NRAS*, or *BRAF* genes might also be tested for changes in the *NTRK* genes. These gene changes can lead to abnormal cell growth. For cancers that have one of these gene changes, drugs that target the proteins coded for by the *NTRK* genes might be helpful.

MSI and MMR testing: Colorectal cancer cells are also typically tested to see if they have high numbers of gene changes called *microsatellite instability* (MSI). Testing might also be done to check for changes in any of the mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) or the proteins they encode. *EPCAM*, another gene, is also routinely checked.

Changes in MSI or in MMR genes (or both) are often seen in people with Lynch syndrome (HNPCC). Most colorectal cancers do not have high levels of MSI or changes in MMR genes. But most colorectal cancers that are linked to Lynch syndrome do.

There are 2 possible reasons to test colorectal cancers for MSI or for MMR gene changes:

* To determine if certain immunotherapy drugs might be options for treatment
* To identify people who should be tested for Lynch syndrome. People with Lynch syndrome are at higher risk for some other cancers, so they are typically advised to get other cancer screenings (for example, women with Lynch syndrome may need to be screened for endometrial cancer). Also, if a person has Lynch syndrome, their relatives could have it as well, and may want to be tested for it.

## **Imaging tests to look for colorectal cancer**

Imaging tests use sound waves, x-rays, magnetic fields, or radioactive substances to create pictures of the inside of your body. Imaging tests may be done for a number of reasons, such as:

* To look at suspicious areas that might be cancer
* To learn how far cancer might have spread
* To help determine if treatment is working
* To look for signs of cancer coming back after treatment

### **Computed tomography (CT or CAT) scan**

A CT scan uses x-rays to make detailed cross-sectional images of your body. This test can help tell if colorectal cancer has spread to nearby lymph nodes or to your liver, lungs, or other organs.

CT-guided needle biopsy: If a biopsy is needed to check for cancer spread, this test can also be used to guide a biopsy needle into the mass (lump) to get a tissue sample to check for cancer.

### **Ultrasound**

Ultrasound uses sound waves and their echoes to create images of the inside of the body. A small microphone-like instrument called a transducer gives off sound waves and picks up the echoes as they bounce off organs. The echoes are converted by a computer into an image on a screen.

Abdominal ultrasound: For this exam, a technician moves the transducer along the skin over your abdomen. This type of ultrasound can be used to look for tumors in your liver, gallbladder, pancreas, or elsewhere in your abdomen, but it can’t look for tumors of the colon or rectum.

Endorectal ultrasound: This test uses a special transducer that is inserted into the rectum. It is used to see how far through the rectal wall a cancer has grown and whether it has reached nearby organs or lymph nodes.

Intraoperative ultrasound: This exam is done during surgery. The transducer is placed directly against the surface of the liver, making this test very useful for detecting the spread of colorectal cancer to the liver. This allows the surgeon to biopsy the tumor, if one is found, while the patient is asleep.

### **Magnetic resonance imaging (MRI) scan**

Like CT scans, MRI scans show detailed images of soft tissues in the body. But MRI scans use radio waves and strong magnets instead of x-rays. A contrast material called *gadolinium* may be injected into a vein before the scan to get clear pictures.

MRI can be used to look at abnormal areas in the liver or the brain and spinal cord that could be cancer spread.

Endorectal MRI: An MRI scan of the pelvis can be used in patients with rectal cancer to see if the tumor has spread into nearby structures. To improve the accuracy of the test, some doctors use an endorectal MRI. For this test, the doctor places a probe, called an *endorectal coil*, inside the rectum. This stays in place for 30 to 45 minutes during the test and might be uncomfortable. The endorectal MRI helps stage rectal cancer and guides decision-making in regard to surgery and treatment.

### **Chest x-ray**

An x-ray might be done after colorectal cancer has been diagnosed to see if cancer has spread to the lungs, but more often a CT scan of the lungs is done since it tends to give more detailed pictures.

### **Positron emission tomography (PET) scan**

For a PET scan, a slightly radioactive form of sugar (known as FDG) is injected into the blood and collects mainly in cancer cells. PET scans are generally done to help see if the cancer has spread to other parts of the body, outside of the colon or rectum. However, they do not show if cancer has spread to the brain.

### **Angiography**

Angiography is an x-ray test for looking at blood vessels. A contrast dye is injected into an artery, and then x-rays are taken. The dye outlines the blood vessels on x-rays.

If your cancer has spread to the liver, this test can show the arteries that supply blood to those tumors. This can help surgeons decide if the liver tumors can be removed and if so, it can help plan the operation. Angiography can also help in planning other treatments for cancer spread to the liver, like embolization.

# **Surgery for Rectal Cancer**

Surgery is usually the main treatment for rectal cancer. Radiation and chemotherapy are often given before or after surgery. The type of surgery used depends on the stage (extent) of the cancer, where it is, and the goal of the surgery.

## **Determining surgery options**

Before doing surgery, the doctor will need to know how close the tumor is to the anus. This will help decide what type of surgery is done. It can also impact outcomes if the cancer has spread to the ring-like muscles around the anus (anal sphincter) that keep stool from coming out until they relax during a bowel movement.

## **Polypectomy and local excision**

Some early-stage rectal cancers and most polyps can be removed during a colonoscopy. This is a procedure that uses a long, flexible tube with a small video camera on the end that’s put into the person’s anus and threaded into the rectum. These surgeries can be done during a colonoscopy:

* For a polypectomy, the cancer is removed as part of the polyp, which is cut at its base (the part that looks like the stem of a mushroom). This is usually done by passing a wire loop through the colonoscope to cut the polyp from the wall of the rectum with an electric current.
* A local excision is a slightly more involved procedure. Tools are used through the colonoscope to remove small cancers on the inside lining of the rectum, along with a small amount of surrounding healthy tissue on the wall of rectum.

When cancer or polyps are taken out this way, the doctor doesn’t have to cut into the abdomen (belly) from the outside. The goal of these surgeries is to remove the cancer or polyp in one piece. If some cancer is left behind or if, based on lab tests, the tumor is thought to have a chance to spread, a more complex type of rectal surgery (see below) might be the next step.

## **Transanal excision (TAE)**

This surgery can be used to remove some early-stage I rectal cancers that are relatively small and not too far from the anus. As with polypectomy and local excision, TAE is done with instruments that are put into the rectum through the anus. The skin over the abdomen (belly) isn’t cut. TAE is usually done with local anesthesia (numbing medicine); the patient is not asleep during the operation.

In this operation, the surgeon cuts through all layers of the rectal wall to take out the cancer, as well as some surrounding normal rectal tissue. The hole in the rectal wall is then closed.

Lymph nodes are not removed during this surgery, so radiation with or without chemotherapy might be recommended after surgery if the cancer has grown deep into the rectum, was not removed completely, or has signs of spread into the lymph system or blood vessels. Sometimes, instead of chemo and radiation, a more extensive surgery, such as low anterior resection (LAR) or abdominoperineal resection (APR) (discussed below), might be recommended and then followed with chemo and radiation.

## **Transanal endoscopic microsurgery (TEM)**

This operation can sometimes be used for early-stage I cancers that are higher in the rectum and can’t be reached using the standard transanal resection (see above). A specially designed magnifying scope is put through the anus and into the rectum. This allows the surgeon to do a transanal resection with great precision and accuracy. This operation requires special equipment and surgeons with special training and experience.

## **Low anterior resection (LAR)**

For patients with a cT2-4 rectal cancer who has a normal functioning anorectal sphincter (the muscle that keeps the anus closed and prevents stool leakage), a low anterior resection (LAR) may be recommended, with the goal to preserve the sphincter function.

A low anterior resection is done with general anesthesia (where the patient is put into a deep sleep). The surgeon makes several small incisions (cuts) in the abdomen. The cancer and a margin (edge or rim) of normal tissue around the cancer is removed, along with nearby lymph nodes and other tissues around the rectum.

The colon is then reattached to the remaining rectum so that a permanent colostomy is not needed. A colostomy is needed when, instead of reconnecting the colon and rectum, the top end of the colon is attached to an opening made in the skin of the abdomen. Stool then comes out this opening.

If radiation and chemotherapy have been given before surgery, it’s common for a short-term ileostomy to be made. (This is where the end of the ileum, the last part of the small intestine, is connected to a hole in the skin of the abdomen.) This gives the rectum time to heal before stool moves through it again. In most cases, the ileostomy can be reversed (the intestines reconnected) about 8 weeks later.

Most patients spend several days in the hospital after the LAR, depending on how the surgery was done and their overall health. It could take 3 to 6 weeks to recover at home.

## **Proctectomy with coloanal anastomosis**

Some stage I and most stage II and III rectal cancers in the middle and lower third of the rectum require removing the entire rectum (called a proctectomy). The rectum has to be removed so that a total mesorectal excision (TME) can be done to remove all of the lymph nodes near the rectum. The colon is then connected to the anus (called a colo-anal anastomosis) so that the patient will pass stool in the usual way.

Sometimes when a colo-anal anastomosis is done, a small pouch is made by doubling back a short piece of colon (called a colonic J-pouch) or by enlarging a segment of the colon (called coloplasty). This small reservoir or pouch of colon provides storage for stool, like the rectum did before surgery.

When special techniques are needed to avoid a permanent colostomy, the patient may need a short-term ileostomy (where the end of the ileum, the last part of the small intestine, is connected to a hole in the abdominal skin) for about 8 weeks while the bowel heals. A second operation is then done to reconnect the intestines and close the ileostomy opening.

General anesthesia (where the patient is put into a deep sleep) is used for this operation. Most patients spend several days in the hospital after surgery, depending on how it was done and their overall health. It could take 3 to 6 weeks to recover at home.

## **Abdominoperineal resection (APR)**

This operation is more involved than the LAR. For patients with a cT2-4 rectal cancer that is unable to be fully removed without affecting the sphincter, an APR may be recommended. It’s often needed if the cancer is growing into the sphincter muscle (the muscle that keeps the anus closed and prevents stool leakage) or the nearby muscles that help control urine flow (called levator muscles).

Here, the surgeon makes a cut or incision (or several small incisions) in the skin of the abdomen, and another in the skin around the anus. This allows the surgeon to remove the rectum, the anus, and the tissues around it, including the sphincter muscle. Because the anus is removed, a permanent colostomy is needed (the end of the colon is connected to a hole in the skin over the abdomen) to allow stool to pass.

General anesthesia (where the patient is put into a deep sleep) is used for this operation. Most people spend several days in the hospital after an APR, depending on how the surgery is done and their overall health. Recovery time at home may be 3 to 6 weeks.

## **Pelvic exenteration**

For patients with T4 rectal cancer (where the rectal cancer is growing into nearby organs, and no evidence of metastatic disease, a pelvic exenteration (or multivisceral resection) may be recommended. This is a major surgery and is not commonly done. The surgeon will remove the rectum as well as any nearby organs that the cancer has reached, such as the bladder, prostate (in men), or uterus (in women).

A colostomy is needed after pelvic exenteration. If the bladder is removed, a urostomy is needed, too. (This is an opening in skin of the abdomen where urine leaves the body and is held in a pouch that sticks to the skin.) It can take many months to fully recover from this complicated surgery.

## **Diverting colostomy**

Some patients have rectal cancer that has spread and is also blocking the rectum. In this case, surgery may be done to relieve the blockage without removing the part of the rectum containing the cancer. Instead, the colon is cut above the cancer and attached to a stoma (an opening in the skin of the abdomen) to allow stool to come out. This is called a diverting colostomy. It can often help the patient recover enough to start other treatments (such as chemotherapy).

## **Surgery for rectal cancer spread**

If rectal cancer has spread and formed just one or a few tumors in the lungs or liver (and nowhere else), surgery might be used to remove it. In most cases, this is only done if the cancer in the rectum is also being removed (or was already removed). Depending on the extent of the cancer, this might help the patient live longer, or it could even cure the cancer. Deciding if surgery is an option to remove areas of cancer spread depends on their size, number, and location.

## **Possible side effects of rectal surgery**

Possible risks and side effects of surgery depend on several factors, including the extent of the operation and a person’s general health before surgery. Problems during or shortly after the operation can include bleeding from the surgery, infections at the surgery site, and blood clots in the legs.

When you wake up after surgery, you will have some pain and will need pain medicines for a few days. For the first couple of days, you may not be able to eat, or you may be allowed limited liquids, as the rectum needs some time to recover. Most people are able to eat solid food again in a few days.

Rarely, the new connections between the ends of the colon may not hold together and may leak. This can quickly cause severe belly pain, fever, and the belly to feel very hard. A smaller leak may cause you to not pass stool, have no desire to eat, and not do well or recover after surgery. A leak can lead to infection, and more surgery may be needed to fix it. It’s also possible that the incision (cut) in the abdomen (belly) might open up, becoming an open wound that may need special care as it heals.

After the surgery, you might develop scar tissue in your abdomen (belly) that can cause organs or tissues to stick together. These are called *adhesions*. Normally, your intestines freely slide around inside your belly. In rare cases, adhesions can cause the bowels to twist up and can even block the bowel. This causes pain and swelling in the belly that’s often worse after eating. Further surgery may be needed to remove the scar tissue.

## **Colostomy or ileostomy**

Some people need a temporary or permanent colostomy (or ileostomy) after surgery. This may take some time to get used to and may require some lifestyle adjustments. If you have a colostomy or ileostomy, you will need to learn how and where to order the proper supplies and how to manage it. Specially trained ostomy nurses or enterostomal therapists can help you. They’ll usually see you in the hospital before your operation to discuss the ostomy and to mark a site for the opening. After your surgery, they may come to your home or an outpatient setting to give you more training. There may also be ostomy support groups you can be part of. This is a good way to learn from others with firsthand experience in managing this part of the treatment.

## **Sexual function and fertility**

Rectal surgery has been linked to sexual problems and quality-of-life issues. Talk to your doctor about how your body will look and work after surgery. Ask how surgery will impact your sex life. You and your partner should know what you can expect. For example:

* If you are a man, an abdominoperineal resection (APR) may stop your erections or your ability to reach an orgasm. In other cases, your pleasure at orgasm may become less intense. Normal aging may cause some of these changes, but they may be made worse by the surgery.  
  An APR can also affect fertility. Talk with your doctor if you think you want to father a child in the future. There may still be ways to do this.
* If you are a woman, rectal surgery (except pelvic exenteration) usually doesn’t cause any loss of sexual function. Abdominal adhesions (scar tissue) may sometimes cause pain or discomfort during sex. If your uterus is removed, you won't be able to get pregnant.

If you have a colostomy, it can have an impact on body image and sexual comfort level . While it may require some adjustments, it should not keep you from having an enjoyable sex life.

**TREATMENT**

## **Ablation**

Ablation techniques are used to destroy small tumors (less than 4 cm across) instead of removing them with surgery. There are many different types of ablation techniques. They can be used to treat tumors in other places, too.

### **Radiofrequency ablation (RFA)**

Radiofrequency ablation is one of the most common methods to treat cancer that has spread to the liver. It uses high-energy radio waves to kill cancer cells. A CT scan or ultrasound is used to guide a thin, needle-like probe through the skin and into the tumor. An electric current is then sent to the tip of the probe, releasing high-frequency radio waves that heat the tumor and destroy the cancer cells.

### **Microwave ablation (MWA)**

The microwave ablation method is used to treat cancer that has spread to the liver. Imaging tests are used to guide a needle-like probe into the tumor. Electromagnetic microwaves are then sent through it to create high temperatures that kill the cancer quickly. This treatment has been used to treat larger cancers (up to 6 cm across).

### **Percutaneous ethanol ablation (PEI) or Alcohol ablation**

Percutaneous ethanol injectiondestroys the cancer cells by injectingconcentrated alcohol into the tumor. This is usually done through the skin using a needle, which is guided by ultrasound or CT scans. Sometimes multiple treatments of PEI may be needed to treat the whole tumor.

### **Cryoablation**

Cryoablation destroys the tumor by freezing it with a thin metal probe. The probe is guided through the skin and into the tumor using ultrasound. Then very cold gas (usually liquid nitrogen or argon gas) is passed through the end of the probe to freeze the tumor, killing the cancer cells. This method can treat larger tumors than the other ablation techniques, but sometimes general anesthesia (drugs used to put the patient into a deep sleep) is needed. Treatment can be repeated as needed to kill all the cancer cells.

### **Side effects of ablation therapy**

Possible side effects after ablation therapy include:

* Abdominal (belly) pain
* Infection in the liver
* Fever
* Bleeding into the chest cavity or abdomen
* Abnormal liver tests.

Serious complications are rare, but they are possible.

## **Embolization**

Embolization is used to treat tumors in the liver. In an embolization procedure, a substance is injected directly into an artery in the liver to block or reduce the blood flow to the tumor.

The liver is special in that it has 2 blood supplies. Most normal liver cells get blood from the portal vein, but cancer cells in the liver usually get their blood supply from the hepatic artery. Blocking the part of the hepatic artery that feeds the tumor helps kill the cancer cells, and it leaves most of the healthy liver cells unharmed because they get their blood supply from the portal vein.

Embolization can be used to treat tumors larger than 5 cm (about 2 inches) across that are often too big to be treated with ablation. It can also be used along with ablation. Embolization does reduce some of the blood supply to the normal liver tissue, so it may not be a good option for patients with liver damage from diseases like hepatitis or cirrhosis.

There are 3 main types of embolization procedures used to treat colon or rectal cancer that has spread (metastasized) to the liver:

* Arterial embolization is also called trans-arterial embolization or TAE. In this procedure, a catheter (a thin, flexible tube) is put into an artery through a small cut in the inner thigh and eased up into the hepatic artery in the liver. A dye is usually injected into the blood to help the doctor watch the path of the catheter using x-ray pictures. Once the catheter is in the right place, small particles are injected into the artery to plug it up, blocking oxygen and key nutrients from the cancer.
* Chemoembolization (also called trans-arterial chemoembolization or TACE*)* combines arterial embolization with chemotherapy. TACE is done by giving chemotherapy through a catheter that’s put right into the artery that feeds the tumor, then plugging up the artery so the chemo can stay close to the tumor. Multiple treatments may be given over 4 to 6 weeks.
* Radioembolization combines embolization and radiation therapy. This is done by injecting tiny beads (called microspheres) coated with radioactive yttrium-90 (Y-90) into the hepatic artery. The beads lodge in the blood vessels near the tumor where they give off small amounts of radiation to the tumor site for several days. The radiation travels a very short distance, so its effects are limited mainly to the tumor.

### **Possible side effects of embolization**

Possible side effects after embolization include:

* Abdominal (belly) pain
* Infection in the liver
* Fever
* Gallbladder inflammation
* Blood clots in the main blood vessels of the liver
* Abnormal liver tests

Because healthy liver tissue can be affected, there is a risk that liver function will get worse after embolization. This risk is higher if a large branch of the hepatic artery is embolized. Serious complications are not common, but they are possible.

## **Radiation therapy for rectal cancer**

For rectal cancer, radiation therapy is a more common treatment and may be used:

* Either before and/or after surgery, often along with chemotherapy, to help keep the cancer from coming back. Many doctors now favor giving radiation therapy before surgery, as it may make it easier to remove the cancer, especially if the cancer's size and/or location might make surgery difficult. This is called neoadjuvant treatment. Giving chemoradiation before surgery can also help lower the chances of damaging the sphincter muscles in the rectum when surgery is done. In either case, nearby lymph nodes are usually treated too.
* During surgery, right to the area where the tumor was, to kill any rectal cancer cells that may be left behind. This is called intraoperative radiation therapy or IORT.
* With or without chemo to help control rectal cancer if a person is not healthy enough for surgery or to ease symptoms if advanced rectal cancer is causing intestinal blockage, bleeding, or pain.
* To re-treat rectal tumors that come back in the pelvis after radiation was given.
* To help treat rectal cancer that has spread to other areas, such as the bones, lungs, or brain.

## **Types of radiation therapy**

Different types of radiation therapy can be used to treat colon and rectal cancers.

### **External-beam radiation therapy (EBRT)**

EBRT is the type of radiation therapy used most often for people with colon or rectal cancer. The radiation is focused on the cancer from a machine outside the body. It’s a lot like getting an x-ray, but the radiation is more intense. How often and how long a person gets radiation treatments depends on the reason the radiation is being given and other factors. Treatments might be given over the course of a few days or several weeks.

Newer EBRT techniques, such as three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), and stereotactic body radiation therapy (SBRT), have been shown to help doctors treat colorectal cancers that have spread to the lungs or liver more accurately while lowering the radiation exposure to nearby healthy tissues. They are typically used if there are only a small number of tumors and if the tumors are causing symptoms and surgery is not an option.

### **Internal radiation therapy (brachytherapy)**

Brachytherapy might be used to treat some rectal cancers, but more research is needed to understand how to best use and when to use brachytherapy.

For this treatment, a radioactive source is put inside your rectum next to or into the tumor. This allows the radiation to reach the rectum without passing through the skin and other tissues of the belly (abdomen), so it’s less likely to damage nearby tissues.

Endocavitary radiation therapy: For this treatment, a small balloon-like device is placed into the rectum to deliver high-intensity radiation for a few minutes. This is typically done in 4 treatments (or less), with about 2 weeks between each treatment. This can let some patients, particularly elderly patients, avoid major surgery and a colostomy. This type of treatment is used for some small rectal cancers or in cases where radiation was already given in the pelvic area and the rectal cancer has come back. Sometimes external-beam radiation therapy is also given.

Interstitial brachytherapy: For this treatment, a tube is placed into the rectum and right into the tumor. Small pellets of radioactive material are then put into the tube for several minutes. The radiation travels only a short distance, limiting the harmful effects on nearby healthy tissues. It’s sometimes used to treat people with rectal cancer who are not healthy enough for surgery or have cancer that has come back in the rectum. This can be done a few times a week for a couple of weeks, but it can also be just a one-time procedure.

### **Radioembolization**

Radiation can also be given during an embolization procedure.

### **Possible side effects of radiation therapy**

If you’re going to get radiation therapy, it’s important to ask your doctor about the possible short- and long-term side effects so that you know what to expect. Possible side effects of radiation therapy for colon and rectal cancer can include:

* Skin irritation at the site where radiation beams were aimed, which can range from redness to blistering and peeling
* Problems with wound healing if radiation was given before surgery
* Nausea
* Rectal irritation, which can cause diarrhea, painful bowel movements, or blood in the stool
* Bowel incontinence (stool leakage)
* Bladder irritation, which can cause problems like feeling like you have to go often (called frequency), burning or pain while urinating, or blood in the urine
* Fatigue/tiredness
* Sexual problems (erection issues in men and vaginal irritation in women)
* Scarring, fibrosis (stiffening), and adhesions that cause the tissues in the treated area to stick to each other

Most side effects should get better over time after treatment ends, but some problems may not go away completely. If you notice any side effects, talk to your doctor right away so steps can be taken to reduce or relieve them.

## **chemotherapy used?**

Chemo may be used at different times during treatment for colorectal cancer:

* Neoadjuvant chemo is given (sometimes with radiation) before surgery to try to shrink the cancer and make it easier to remove. This is often done for rectal cancer.
* Adjuvant chemo is given after surgery. The goal is to kill cancer cells that might have been left behind at surgery because they were too small to see, as well as cancer cells that might have escaped from the main colon or rectal cancer to settle in other parts of the body but are too small to see on imaging tests. This helps lower the chance that the cancer will come back.
* For advanced cancers that have spread to other organs like the liver, chemo can be used to help shrink tumors and ease problems they’re causing. While it’s not likely to cure the cancer, this often helps people feel better and live longer.

## **How is chemotherapy given?**

You can get chemotherapy in different ways to treat colorectal cancer.

* Systemic chemotherapy: Drugs are put into your blood through a vein or you take them by mouth. The drugs enter your bloodstream and reach almost all areas of your body.
* Regional chemotherapy: Drugs are put into an artery that leads to the part of the body with the cancer. This focuses the chemo on the cancer cells in that area. It reduces side effects by limiting the amount of drug reaching the rest of your body. Hepatic artery infusion, or chemo given directly into the hepatic artery, is an example of regional chemotherapy sometimes used for cancer that has spread to the liver.

Chemo drugs for colon or rectal cancer that are given into a vein (IV), can be given either as an injection over a few minutes or as an infusion over a longer period of time. This can be done in a doctor’s office, infusion center, or in a hospital setting.

Often, a slightly larger and sturdier IV is required in the vein system to administer chemo. These are known as central venous catheters (CVCs), central venous access devices (CVADs), or central lines. They are used to put medicines, blood products, nutrients, or fluids into your blood. They can also be used to take blood for testing. There are many different kinds of CVCs. The most common types are the tunneled central lines, ports, and peripherally inserted central catheter (PICC) lines.

Chemo is given in cycles, which include a rest period to give you time to recover from the effects of the drugs. Each cycle is usually 2 or 3 weeks long. The schedule varies depending on the drugs used. For example, with some drugs, the chemo is given only on the first day of the cycle. With others, it is given for a few days in a row, or once a week. Then, at the end of the cycle, the chemo schedule repeats to start the next cycle.

Adjuvant or neoadjuvant chemo is often given for a total of 3 to 6 months, depending on the drugs used. The length of treatment for advanced colorectal cancer depends on how well it is working and what side effects you have.

## **Chemotherapy drugs used to treat colorectal cancer**

Some drugs commonly used for colorectal cancer include:

* 5-Fluorouracil (5-FU)
* Capecitabine (Xeloda), a pill that is changed into 5-FU once it gets to the tumor
* Irinotecan (Camptosar)
* Oxaliplatin (Eloxatin)
* Trifluridine and tipiracil (Lonsurf), a combination drug in pill form

Most often, combinations of 2 or 3 of these drugs are used. Sometimes, chemo drugs are given along with a targeted therapy drug.

## **Possible side effects of chemo**

Chemo drugs attack cells that are dividing quickly, which is why they work against cancer cells. But other cells in the body, such as those in hair follicles and in the lining of the mouth and intestines, are also dividing quickly. These cells can be affected by chemo too, which can lead to side effects.

The side effects of chemo depend on the type and dose of drugs given and how long you take them. Common side effects of chemo can include:

* Hair loss
* Mouth sores
* Loss of appetite or weight loss
* Nausea and vomiting
* Diarrhea
* Nail changes
* Skin changes

Chemo can also affect the blood-forming cells of the bone marrow, which can lead to:

* Increased chance of infections (from low white blood cell counts)
* Easy bruising or bleeding (from low blood platelet counts)
* Fatigue (from low red blood cell counts and other reasons)

Other side effects are specific to certain drugs. Ask your cancer care team about the possible side effects of the specific drugs you are getting. For example:

* Hand-foot syndrome can develop during treatment with capecitabine or 5-FU. It can start out as redness in the hands and feet, and then might progress to pain and sensitivity in the palms and soles. If it worsens, the skin may blister or peel, sometimes leading to painful sores. It’s important to tell your doctor right away about any early symptoms, such as redness or sensitivity, so that steps can be taken to keep things from getting worse.
* Neuropathy (nerve damage) is a common side effect of oxaliplatin. Symptoms include numbness, tingling, and even pain in the hands and feet. It can also cause intense sensitivity to cold in your throat, esophagus (the tube connecting the throat to the stomach), and the palms of your hands. This can cause pain when swallowing cold liquids or holding a cold glass. If you'll be getting oxaliplatin, talk with your doctor about side effects beforehand, and let them know right away if you develop numbness and tingling or other side effects.
* Allergic or sensitivity reactions can happen in some people while getting the drug oxaliplatin. Symptoms can include skin rash; chest tightness and trouble breathing; back pain; or feeling dizzy, lightheaded, or weakness. Be sure to tell your nurse right away if you notice any of these symptoms while you're getting chemo.
* Diarrhea is a common side effect with many of these chemo drugs, but can be particularly bad with irinotecan. It needs to be treated right away – at the first loose stool – to prevent severe dehydration. This often means taking a drug like loperamide (Imodium) or even being admitted to the hospital for intravenous hydration. If you're getting a chemo drug that will likely cause diarrhea, your doctor will give you instructions on what drugs to take and how often to take them to control this problem.

Most of these side effects tend to go away over time after treatment ends. Some, such as hand and foot numbness from oxaliplatin, may last for a long time. There are often ways to lessen these side effects. For example, you can be given drugs to help prevent or reduce nausea and vomiting, or you may be told to keep ice chips in your mouth while chemo is being given to lower the chances of getting mouth sores.

Be sure to discuss any questions about side effects with your cancer care team. Also report any side effects or changes you notice while getting chemo so that they can be treated right away. In some cases, the doses of the chemo drugs may need to be reduced or treatment may need to be delayed or stopped to help keep the problem from getting worse.

## **Treating stage 0 rectal cancer**

Stage 0 rectal cancers have not grown beyond the inner lining of the rectum. Removing or destroying the cancer is typically all that’s needed. You can usually be treated with surgery, such as a polypectomy (removing the polyp), local excision, or transanal resection. In rare cases, a more extensive surgery might be needed.

## **Treating stage I rectal cancer**

Stage I rectal cancers have grown into deeper layers of the rectal wall but have not spread outside the rectum itself.

This stage includes cancers that were part of a polyp. If the polyp is removed completely during colonoscopy, with no cancer at the edges, no other treatment may be needed. If the cancer in the polyp was high grade, or if there were cancer cells at the edges of the polyp, you might be advised to have more surgery. More surgery may also be advised if the polyp couldn’t be removed completely or if it had to be removed in many pieces, making it hard to see if there were cancer cells at the edges (margins).

For other stage I cancers, surgery is usually the main treatment. Some small stage I cancers can be removed through the anus without cutting the abdomen (belly), using transanal resection or transanal endoscopic microsurgery (TEM). For some, a low anterior resection (LAR), proctectomy with coloanal anastomosis, or an abdominoperineal resection (APR) may be needed, depending on exactly where the cancer is located within the rectum.

Additional treatment typically isn’t needed after these operations, unless the surgeon finds the cancer is more advanced than was thought before surgery. If it is more advanced, a combination of chemo and radiation therapy is usually given. 5-FU and capecitabine are the chemo drugs most often used.

If you’re not healthy enough to have surgery, you may be treated with chemotherapy given with radiation therapy.

## **Treating stage II rectal cancer**

Many stage II rectal cancers have grown through the wall of the rectum and might extend into nearby tissues. They have not spread to the lymph nodes.

For treatment of stage II rectal cancer that is pMMR or MSS, chemotherapy, radiation therapy, and surgery are usually given, although the order of these treatments might be different for some people. Recent studies have shown that an approach called total neoadjuvant therapy (TNT) may be effective and potentially allow people from having to undergo transabdominal surgery. TNT is when a patient is treated with both chemotherapy and radiation before surgery. Here is a common approach to treating these cancers:

* Many people get both chemo and radiation therapy (called chemoradiation) as their first treatment. The chemo given with radiation is usually either 5-FU or capecitabine .
* This may be followed by more chemotherapy (without radiation) for several months. The chemo may be the FOLFOX regimen (oxaliplatin, 5-FU, and leucovorin) or CAPEOX (capecitabine plus oxaliplatin) based on what’s best suited to your health needs.
* Afterward, surgery, such as a low anterior resection (LAR), proctectomy with coloanal anastomosis, or abdominoperineal resection (APR), may be done, depending on where the cancer is in the rectum. If the chemo and radiation therapy shrink the tumor enough, sometimes a transanal resection can be done instead of a more invasive LAR or APR. This might help you avoid having a colostomy. But not all doctors agree with this method, because it doesn’t let the surgeon check the nearby lymph nodes for cancer.
* Another option might be to get chemotherapy alone, followed by chemoradiation followed by surgery.

For treatment of stage II rectal cancer that is dMMR or MSI-H, immunotherapy is preferred, but chemotherapy combined with radiation (TNT) is also an option. If you and your doctor choose to be treated with immunotherapy, it is usually given for 6 months. If there are no findings of cancer after the immunotherapy treatment by imaging and scope, no further therapy is given. If there are findings of persistent cancer after the immunotherapy treatment, combined chemo and radiation may then be given, followed by surgery.

## **Treating stage III rectal cancer**

Stage III rectal cancers have spread to nearby lymph nodes but not to other parts of the body.

Treatment for stage III rectal cancer is very similar to that of stage II rectal cancer (see above).

## **Treating stage IV rectal cancer**

Stage IV rectal cancers have spread to distant organs and tissues, such as the liver or lungs. Treatment options for stage IV rectal cancer is very similar to that of Stage IV colon cancer. . For rectal cancers that don’t shrink with chemo and widespread cancers that are causing symptoms, treatment is done to relieve symptoms and avoid long-term problems, such as bleeding or blockage of the intestines. Treatments may include one or more of these:

* Removing the rectal cancer with surgery
* Surgery to create a colostomy and bypass the rectal cancer (a diverting colostomy)
* Using a special laser to destroy the cancer within the rectum
* Placing a stent (hollow metal tube) within the rectum to keep it open; this does not require surgery
* Chemoradiation therapy
* Chemo alone

## **Treating recurrent rectal cancer**

Recurrent cancer means that the cancer has come back after treatment. It may come back near the area of the initial rectal cancer (locally) or in distant organs, like the lungs or liver. If the cancer does recur, it’s usually in the first 2 to 3 years after surgery, but it can also recur much later.

### **Local recurrence**

If the cancer comes back in the pelvis (locally), it’s treated with surgery to remove the cancer, if possible. This surgery is often more extensive than the initial surgery. In some cases, radiation therapy may be given during the surgery (this is called intraoperative radiotherapy) or afterward. Chemo may also be given after surgery. Radiation therapy might be used as well if it was not used before.

### **Distant recurrence**

If the cancer comes back in a distant part of the body, the treatment will depend on whether it can be removed by surgery.

If the cancer can be removed, surgery is done. Chemo may be given before or after surgery, too. When the cancer has spread to the liver, chemo may be given through the hepatic artery leading to the liver.

If the cancer can’t be removed by surgery, chemo and/or targeted therapy drugs may be used. For people with certain gene changes in their cancer cells, another option might be treatment with immunotherapy. The drugs used will depend on what drugs a person has received previously and on their overall health. If the cancer doesn’t shrink, a different drug combination may be tried.

As with stage IV rectal cancer, surgery, radiation therapy, or other approaches may be used at some point to relieve symptoms and avoid long-term problems, such as bleeding or blockage of the intestines.

These cancers can often be hard to treat, so you might also want to ask your doctor if there are any clinical trials of newer treatments that might be right for you.

## **Immune checkpoint inhibitors**

For people with either early- or advanced-stage colorectal cancer, immunotherapy is now a cornerstone of treatment if the tumor has findings of dMMR (deficient mismatch repair) or MSI-H (microsatellite instability-high).

An important part of the immune system is its ability to keep itself from attacking the body’s normal cells. To do this, it uses “checkpoints” – proteins on immune cells that need to be turned on (or off) to start an immune response. Colorectal cancer cells sometimes use these checkpoints to avoid being attacked by the immune system. Drugs that target these checkpoints help to restore the immune response against colorectal cancer cells.

Drugs called checkpoint inhibitors can be used for people whose colorectal cancer cells have tested positive for specific gene changes, specifically a high level of microsatellite instability (MSI-H), or changes in one of the mismatch repair (MMR) genes. These drugs might be given to people before surgery for early-stage colon cancer, or to treat people whose cancer can’t be removed with surgery, has come back (recurred) after treatment, or has spread to other parts of the body (metastasized).

### **PD-1 inhibitors**

Pembrolizumab (Keytruda), nivolumab (Opdivo), and Dostarlimab (Jemperli) are drugs that target PD-1, a protein on immune system cells called T cells that normally help keep these cells from attacking other cells in the body. By blocking PD-1, these drugs boost the immune response against colorectal cancer cells. They are only given if the tumor has had findings of dMMR or MSI-H.

Pembrolizumab can be given alone. It is given as an intravenous (IV) infusion every 3 or 6 weeks.

Nivolumab can be given alone or with ipilimumab (see below). It can be given by itself as an IV infusion every 2 or 4 weeks. If it is used along with ipilimumab, then it is typically given every 3 weeks.

Dostarlimab can be given alone. It is given as an intravenous (IV) infusion every 3 weeks for 4 treatments, and then given at a higher dose every 6 weeks. This drug is not approved specifically to treat colorectal cancer at this time. It is approved to treat other types of cancer, but doctors can prescribe it off-label for colorectal cancer. Still, it’s important to check with your insurance provider before getting this drug to make sure it is covered.

### **CTLA-4 inhibitor**

Ipilimumab (Yervoy) is another drug that boosts the immune response, but it has a different target. It blocks CTLA-4, another protein on T cells that normally helps keep them in check.

This drug can be used along with nivolumab (Opdivo) to treat colorectal cancer. It is given as an intravenous (IV) infusion, usually once every 3 weeks for 4 treatments.

## **Possible side effects of immunotherapy**

Side effects of these drugs include fatigue, cough, nausea, diarrhea, skin rash, loss of appetite, constipation, joint pain, and itching.

Other, more serious side effects occur less often.

Infusion reactions: Some people might have an infusion reaction while getting these drugs. This is like an allergic reaction, and can include fever, chills, flushing of the face, rash, itchy skin, feeling dizzy, wheezing, and trouble breathing. It’s important to tell your doctor right away if you have any of these symptoms while getting these drugs.

Autoimmune reactions: These drugs work by basically removing one of the safeguards on the body’s immune system. Sometimes the immune system starts attacking other parts of the body, which can cause serious or even life-threatening problems in the lungs, intestines, liver, hormone-making glands, nerves, skin, kidney, or other organs.

It’s very important to report any new side effects during or after treatment with any of these drugs to your health care team promptly. If serious side effects do occur, you may need to stop treatment and take high doses of corticosteroids to suppress your immune system.

## **When is targeted therapy used?**

Targeted drugs work differently from chemotherapy (chemo) drugs. They sometimes work when chemo drugs don’t, and they often have different side effects. They can be used either along with chemo, by themselves, or in combination with another targeted therapy drug.

Like chemotherapy, these drugs enter the bloodstream and reach almost all areas of the body, which makes them useful against cancers that have spread to distant parts of the body.

Several types of targeted drugs might be used to treat colorectal cancer.

## **Drugs that target blood vessel formation (VEGF)**

Vascular endothelial growth factor (VEGF) is a protein that helps tumors form new blood vessels (a process known as angiogenesis) to get nutrients they need to grow. Drugs that stop VEGF from working can be used to treat some colon or rectal cancers. These include:

* Bevacizumab (Avastin, other names)
* Ramucirumab (Cyramza)
* Ziv-aflibercept (Zaltrap)
* Fruquintinib (Fruzaqla)

Most of these drugs are given as infusions into your vein (IV) every 2 or 3 weeks, in most cases along with chemotherapy. Fruquintinib is given as a capsule and not combined with chemotherapy. These drugs can often help people with advanced colon or rectal cancers live longer.

### **Possible side effects of drugs that target VEGF**

Common side effects of these drugs include:

* High blood pressure
* Protein in the urine
* Bleeding (from the nose or rectum)
* Headaches
* Taste changes
* Skin changes

Rare but possibly serious side effects include blood clots, severe bleeding, holes forming in the colon (called perforations), heart problems, kidney problems, and slow wound healing. If a hole forms in the colon, it can lead to severe infection and surgery may be needed to fix it.

Another rare but serious side effect of these drugs is an allergic reaction during the infusion, which could cause problems with breathing and low blood pressure.

## **Drugs that target cancer cells with EGFR changes**

Epidermal growth factor receptor (EGFR) is a protein that helps cancer cells grow. Drugs that target EGFR (EGFR inhibitors) can be used to treat some advanced colon or rectal cancers. These include:

* Cetuximab (Erbitux)
* Panitumumab (Vectibix)

Both of these drugs are given by infusion into a vein (IV), either once a week or every other week.

These drugs typically don’t work in colorectal cancers that have mutations (defects) in the *KRAS*, *NRAS* or *BRAF* gene. Doctors commonly test the tumor for these gene changes before treatment, and only use these drugs in people whose cancer cells don’t have these mutations.

An exception would be if an EGFR inhibitor is combined with another drug, such as with a BRAF inhibitor (encorafenib, see below) or with a KRAS inhibitor (adagrasib or sotorasib, see below). These two drug combinations appear to have an effect on colon cancer that has been treated with other chemotherapy.

### **Possible side effects of drugs that target EGFR**

The most common side effects of these drugs are skin problems such as an acne-like rash on the face and chest during treatment, which can sometimes lead to infections. An antibiotic and/or steroid cream may be needed to help limit the rash and related infections. Developing this rash often means the cancer is responding to treatment. People who develop this rash often live longer, and those who develop more severe rashes also seem to respond better than those with a milder rash. Other side effects can include:

* Headache
* Tiredness
* Fever
* Diarrhea

A rare but serious side effect of these drugs is an allergic reaction during the infusion, which could cause problems with breathing and low blood pressure. You may be given medicine before treatment to help prevent this. Other serious but rare serious side effects include eye, heart, or lung damage.

## **Drugs that target cells with *BRAF* gene changes**

A small portion of colorectal cancers have changes (mutations) in the *BRAF* gene. Colorectal cancer cells with these changes make an abnormal BRAF protein that helps them grow. Some drugs target this abnormal BRAF protein.

If you have colorectal cancer that has spread, your cancer will likely be tested to see if the cells have a *BRAF* gene change known as BRAF V600E, which can cause the cell to make an abnormal BRAF protein.

Encorafenib (Braftovi) is a BRAF inhibitor, a drug that attacks the abnormal BRAF protein. This drug might be given with an EGFR inhibitor such as cetuximab or panitumumab (see above), possibly along with chemotherapy.

This drug is taken as capsules, once a day.

### **Possible side effects of drugs that target BRAF**

Common side effects of encorafenib, in combination with an EGFR inhibitor, can include skin thickening, diarrhea, rash, loss of appetite, abdominal pain, joint pain, fatigue, and nausea.

Some people treated with a BRAF inhibitor might develop new squamous cell skin cancers. These cancers can often be treated by removing them. Still, your doctor will want to check your skin regularly during treatment and for several months afterward. You should also let your doctor know right away if you notice any new growths or abnormal areas on your skin.

## **Drugs that target cells with HER2 changes**

In a small percentage of people with colorectal cancer, the cancer cells have too much of a growth-promoting protein called HER2 on their surface. Cancers with increased levels of HER2 are called HER2-positive. Drugs that target the HER2 protein can often be helpful in treating these cancers.

Drugs of this type that might be used to treat HER2-positive colorectal cancer include:

* Trastuzumab (Herceptin, other names)
* Pertuzumab (Perjeta)
* Tucatinib (Tukysa)
* Lapatinib (Tykerb)
* Fam-trastuzumab deruxtecan (Enhertu, T-DXd)

For advanced, HER2-positive colorectal cancer that has already been treated with chemotherapy, the most common targeted drug regimens include trastuzumab plus either tucatinib, lapatinib, or pertuzumab. People who might be treated with this regimen must also not have mutations in the *RAS* and *BRAF* genes.

Among these drugs, only tucatinib is FDA approved specifically to treat colorectal cancer at this time, but the others are included in some expert treatment guidelines. Still, it’s important to check with your insurance provider before getting these drugs to make sure they are covered.

### **Possible side effects of drugs that target HER2**

The side effects of HER2-targeted drugs tend to be mild overall, but some can be serious, and different drugs can have different possible side effects. Discuss what you can expect with your doctor.

Some of these drugs can cause heart damage during or after treatment, which might lead to congestive heart failure. Because of this, your doctor will likely check your heart function (with an echocardiogram or a MUGA scan) before treatment, and regularly while you are getting any of these drugs. Let your doctor know if you develop symptoms, such as shortness of breath, a fast heartbeat, leg swelling, and severe fatigue.

Some of these drugs can cause severe diarrhea, so it’s very important to let your health care team know about any changes in bowel habits as soon as they happen.

Lapatinib and tucatinib can also cause hand-foot syndrome, in which the hands and feet become sore and red, and may blister and peel.

Lapatinib and tucatinib can cause liver problems. Your doctor will do blood tests to check your liver function during treatment. Let your health care team know right away if you have possible signs or symptoms of liver problems, such as itchy skin, yellowing of the skin or the white parts of your eyes, dark urine, or pain in the right upper belly area.

Fam-trastuzumab deruxtecan can cause serious lung disease in some people, which might even be life threatening. It’s very important to let your doctor know right away if you’re having symptoms such as coughing, wheezing, trouble breathing, or fever.

## **Drugs that target cells with *NTRK* gene changes**

A very small number of colorectal cancers have changes in one of the *NTRK* genes. This causes them to make abnormal TRK proteins, which can lead to abnormal cell growth and cancer.

Larotrectinib (Vitrakvi), entrectinib (Rozlytrek), and repotrectinib (Augtyro) are drugs that target the TRK proteins. These drugs can be used to treat advanced cancers with *NTRK* gene changes that are still growing despite other treatments.

These drugs are taken as pills or an oral solution, once or twice daily.

### **Possible side effects of TRK inhibitors**

Common side effects of these drugs can include dizziness, fatigue, nausea, vomiting, constipation, weight gain, and diarrhea.

Less common but serious side effects can include abnormal liver tests, increased risk for fractures, heart problems, vision changes, and confusion.

## **Drugs that target cells with *RET* gene changes**

A very small number of colorectal cancers have changes in one of the *RET* genes. This causes them to make abnormal RET proteins, which can lead to abnormal cell growth and cancer.

Selpercatinib (Retevmo) is a drug that targets the RET protein. These drugs can be used to treat advanced cancers with *RET* gene changes that are still growing despite other treatments.

This drug is taken as a capsule twice daily.

This drug is approved to treat other types of cancer, but doctors can prescribe it off-label for colorectal cancer. Still, it’s important to check with your insurance provider before getting these drugs to make sure they are covered.

### **Possible side effects of RET inhibitors**

Common side effects of these drugs can include decrease in white blood cell count and calcium, changes in liver function tests, high blood pressure, fatigue, changes in kidney function, and increased cholesterol.

Less common but serious side effects can include abnormal heart function (QT interval prolongation), bleed, allergic reaction, and inability to heal from a wound.

## **Drugs that target cells with *KRAS* gene changes**

A very small number of colorectal cancers have the *KRAS G12C* gene mutation. This causes them to make abnormal KRAS proteins, which can lead to continued cell growth and cancer.

Adagrasib (Krazati) and Sotorasib (Lumakras) are drugs that target the KRAS proteins. These KRAS inhibitors can be given with an EGFR inhibitor (ie. adagrasib with cetuximab, or sotorasib with panitumumab) to treat advanced cancers with *KRAS* gene changes that are still growing despite other treatments.

These drugs are taken as tablets, once or twice daily.

### **Possible side effects of KRAS inhibitors**

Common side effects of these drugs can include nausea, vomiting, diarrhea, muscle and joint pain, fatigue, decreased appetite, and changes in liver and kidney function.

Less common but serious side effects can include effects to the heart (QTc interval prolongation), liver, and lungs (interstitial lung disease).

## **Other targeted therapy drugs**

Regorafenib (Stivarga) is a type of targeted therapy known as a multikinase inhibitor. Kinases are proteins on or near the surface of a cell that carry important signals to the cell’s control center. Regorafenib blocks several kinase proteins that either help tumor cells grow or help form new blood vessels to feed the tumor. Blocking these proteins can help stop the growth of cancer cells.

This drug can be used to treat advanced colorectal cancer, typically when other drugs are no longer helpful. It’s taken as a pill.

Common side effects include fatigue, rash, hand-foot syndrome (redness and irritation of the hands and feet), diarrhea, high blood pressure, weight loss, and abdominal pain.

Less common but more serious side effects can include confusion, severe bleeding, or perforations (holes) in the stomach or intestines.

## **Diagnostic Considerations**

Other problems to be considered in the differential diagnosis of colon cancer include the following:

* Arteriovenous malformation (AVM)
* Carcinoid/neuroendocrine tumors and rare tumors of the gastrointestinal tract
* Ischemic bowel
* Small-intestine carcinomas
* Gastrointestinal lymphoma

## Differential Diagnoses

* Crohn Disease
* Ileus
* Small Intestinal Diverticulosis
* Ulcerative Colitis

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## **Epidemiology**

The incidence and mortality from colon cancer have been on a slow decline over the past several decades in the United States, with the incidence falling on average 2.4% each year and death rates falling on average 2.2% each year over 2007-2019. However, the overall decline has been driven by a decreasing incidence in individuals age 65 years and older; rates have stabilized in those age 55-64 and have increased by 1% to 2% per year since the mid-1990s in those younger than 55 years of age.

Colorectal cancers remain the third most common cancer in US men and women, the third most common cause of cancer-related mortality in US men, and the fourth most common cause of cancer-related mortality in women. The American Cancer Society estimates that 107,320 new cases of colon cancer will be diagnosed in the United States in 2025. Estimates for mortality from colon and rectal cancer (the two are combined because of classification difficulties) are for 52,900 deaths in 2025.

Worldwide, colon cancer was the fourth most common cancer, with an estimated 1,142,286 million new cases in 2022, and the fifth most common cause of cancer mortality, with 538,167 deaths. Geographically, the incidence varies as much as 10-fold. The highest estimated rates are in Australia–New Zealand, Europe, and Northern America, and the lowest in south-central Asia and middle Africa. Mortality rates worldwide vary six-fold, with the highest estimated mortality rates in southern and eastern Europe and the lowest in south-central Asia and middle Africa.

An epidemiologic study from the European Union (EU) concluded that in 2018, colorectal cancer would account for the second highest number of cancer deaths, at 98,000 deaths in men and 79,400 in women. However, while the total number of colorectal deaths in the EU has risen since 2012 because of the aging population, since 2012 the age-standardized death rate has fallen by 6.7% (to 15.8 per 100,000 in men and 7.5% (to 9.2 per 100,000) in women.

A study by Sung et al that examined colorectal cancer incidence trends in younger adults versus older adults in 50 countries and territories found that from 2013 to 2017, early-onset colorectal cancer (diagnosed at ages 25 to 49 years) increased in 27 countries. The greatest annual increases occurred in New Zealand (3.97%), Chile (3.96%), Puerto Rico (3.81%), and England (3.59%). In 14 of those 27 countries and territories, rates in older adults were either stable or decreased.

### Racial, sexual, and age-related disparities in incidence

Since 1989, colorectal cancer incidence rates have been higher for Blacks than for Whites in both men and women. Currently, incidence rates of colorectal cancer are 21% higher in Black men and 18% higher in Black women compared with White men and women, respectively.

Colorectal mortality rates are 44% higher in Black men and 31% higher in Black women compared with White men and women. However, from 2010 to 2019, colorectal cancer death rates declined faster in Blacks than in Whites (2.8% vs 1.8% per year), narrowing the racial disparity in both men and women.

Asians/Pacific Islanders have the lowest incidence and mortality from colorectal cancer. Hispanics have the second lowest.

The incidence of colorectal cancer is relatively equal in men and women. The American Cancer Society estimates that colon cancer will be diagnosed in 54,510 men and 52,810 women in the United States in 2025.

Age is a well-known risk factor for colorectal cancer, as it is for many other solid tumors. The timeline for progression from early premalignant lesion to malignant cancer ranges from 10-20 years. Median age at diagnosis is 66 years.

However, in contrast to the decline in colon cancer incidence rates in persons age 55 and older, which began in the mid-1980s, rates of colon cancer in younger persons have been increasing. In adults age 20 to 39 years, colon cancer incidence rates have increased by 1.0% to 2.4% annually since the mid-1980s; in those age 40 to 54 years, the incidence has increased by 0.5% to 1.3% annually since the mid-1990s. Currently, adults born circa 1990 have double the risk of colon cancer compared with those born circa 1950. Increased obesity is one likely factor.

From 2011 through 2016, the incidence of colorectal cancer continued to decline in those aged 65 years and older, by 3.3% annually. Rates increased by 1% annually in those aged 50 to 64 years, and rose approximately 2% annually in those younger than 50 years. The American Cancer Society estimated that 17,930 of the 147,950 individuals expected to be diagnosed with colon and rectal cancer in 2020, and 3640 of the 53,200 expected to die from the disease, would be younger than 50 years of age.

Tumor sites tend to vary by patient age. From 2012 to 2016, the proximal colon was the site of colon cancer in 23% of those under 50 years of age, 31% of those 50-64 years, and 49% of those 65 and older. Incidence trends varied by race/ethnicity: in those 50-64 years old, rates increased in Whites by 1.3% per year but decreased in Blacks by 1.6% per year, and were stable in Hispanics. In those younger than 50, rates rose by 2% annually in Whites and by 0.5% annually in Blacks.

A review of Surveillance, Epidemiology and End Results (SEER) data found that US cases of colorectal cancer in persons aged 40-49 years have increased significantly since 1995, with the greatest average annual percentage increase for distant cancers, at 2.9%, while localized and regional disease each increased < 1.5% per year. In addition, the proportion of distant colorectal cancers in this age group increased significantly from 1990-1994 to 2011–2015, from 22% to 27%, while the proportion of localized cases did not change, and the proportion of regional cases decreased. These authors point out that these results indicate a true increase in risk, because if the increase had reflected earlier detection due to wider use of screening, earlier stage at diagnosis would be expected

## **COMMON QUESTIONS AND ANSWERS SET**

## Do I need to get a screening test for colorectal cancer?

If you are at average risk for colorectal cancer, current guidelines recommend starting regular screening at age 45. Screening is important even if you have no symptoms, as it can detect precancerous polyps and early-stage cancers, which are much easier to treat. If you have a family history of colorectal cancer or other risk factors, you may need to start earlier or screen more frequently.

## What screening test(s) do you recommend for me? Why?

For people at average risk, several screening options are available:

* Colonoscopy (every 10 years): The gold standard, as it allows for both detection and removal of polyps in a single procedure.
* Fecal Immunochemical Test (FIT) or Fecal Occult Blood Test (FOBT) (annually): Non-invasive stool tests that look for hidden blood.
* Flexible sigmoidoscopy (every 5 years): Examines the lower part of the colon.
* Stool DNA test with FIT (every 3 years): Checks for DNA changes and blood in the stool.
* CT colonography (every 5 years): A specialized imaging test.

The choice depends on your personal preferences, medical history, and access to testing. Colonoscopy is often recommended because it is the most comprehensive test.

## How do I prepare? Do I need to change my diet or my usual medication before taking the test?

Preparation depends on the test:

* Colonoscopy or sigmoidoscopy: You’ll need to follow a special diet (usually clear liquids) the day before and take a bowel prep to clean out your colon. Some medications may need to be adjusted—your doctor will give you specific instructions.
* Stool tests: Usually require no dietary or medication changes, but follow any instructions provided with the test kit.

## What's involved in the test? Will it be uncomfortable or painful?

* Colonoscopy: You’ll receive sedation to keep you comfortable. Most people don’t feel pain, but you may feel bloated afterward.
* Sigmoidoscopy: Usually less sedation; some discomfort or cramping is possible.
* Stool tests: Done at home, non-invasive, and painless.
* CT colonography: No sedation, but bowel prep is required; some discomfort from air introduced into the colon.

## Is there any risk involved?

All tests carry some risk, but serious complications are rare:

* Colonoscopy: Small risk of bleeding or perforation (tear) in the colon.
* Sigmoidoscopy and CT colonography: Lower risk than colonoscopy.
* Stool tests: No physical risk.

## How much time will I need to take off from work or other responsibilities?

* Colonoscopy: Plan to take the day off for the procedure and recovery from sedation.
* Sigmoidoscopy/CT colonography: May require a few hours off.
* Stool tests: No time off needed; done at home.

## When and from whom will I get results?

* Colonoscopy/sigmoidoscopy: Your doctor will discuss results with you, often the same day for initial findings, with biopsy results in a few days.
* Stool tests: Your healthcare provider will contact you with results, usually within a week.

## Who will do the exam (for colonoscopy or sigmoidoscopy)?

A gastroenterologist or a specially trained physician will perform colonoscopy or sigmoidoscopy procedures

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## **Doctor-Patient Conversation: Colorectal Cancer**

Doctor: Thank you for coming in today. I have your test results, and I’d like to discuss them with you. The diagnosis is colorectal cancer.

Patient: That’s a lot to take in. What does this mean for me?

Doctor: I understand this is difficult news. The next step is to determine the stage of your cancer—how far it has spread. Staging helps us decide on the best treatment options and gives us an idea of your outlook. We’ll use imaging studies and possibly additional tests to get this information.

Patient: What are my treatment options?

Doctor: Treatment depends on the stage and your overall health. For early-stage colorectal cancer, surgery is often the main treatment. If the cancer is more advanced, we may recommend chemotherapy, radiation, targeted therapy, or a combination. We’ll tailor the plan to your specific situation and discuss the benefits and risks of each option.

Patient: Will I need more tests?

Doctor: Yes, we’ll need more imaging and possibly blood tests to complete staging and to check your overall health before starting treatment. After treatment, regular follow-up is important to monitor for recurrence and manage any long-term effects.

Patient: What are the chances the cancer will come back?

Doctor: The risk of recurrence depends on the stage at diagnosis and the type of treatment. Regular follow-up visits, imaging, and lab tests help us detect any recurrence early. We’ll also talk about signs and symptoms to watch for at home.

Patient: How will treatment affect my daily life?

Doctor: Side effects vary depending on the treatment. Surgery may require some recovery time. Chemotherapy can cause fatigue, nausea, or increased risk of infection. We’ll help you manage any side effects and support you throughout your treatment.

Patient: Are there clinical trials or new treatments I should consider?

Doctor: Yes, clinical trials are available for many stages of colorectal cancer. They may offer access to new therapies. We can discuss whether you’re eligible for any trials and what they involve.

Patient: Where can I find support?

Doctor: Our cancer center has social workers and support groups for emotional and practical support. We can also connect you with national organizations and online communities.

Doctor: Please write down any questions you have and bring them to our next visit. We’re here to support you every step of the way.

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**ESOPHAGEAL CANCER**

**DEFINITION AND DESCRIPTION**

Esophageal cancer is a growth of cells that starts in the esophagus. The esophagus is a long, hollow tube that runs from the throat to the stomach. The esophagus helps move swallowed food from the back of the throat to the stomach to be digested.

Esophageal cancer usually begins in the cells that line the inside of the esophagus. Esophageal cancer can happen anywhere along the esophagus.

Esophageal cancer is more common in men. Risk factors include drinking alcohol and smoking.

Esophageal cancer treatment often involves surgery to remove the cancer. Other treatments may include chemotherapy, radiation or a combination of the two. Targeted therapy and immunotherapy also may be used.

**Causes**

Esophageal cancer happens when cells lining the esophagus develop changes in their DNA. A cell's DNA holds the instructions that tell the cell what to do. In healthy cells, the DNA gives instructions to grow and multiply at a set rate. The instructions tell the cells to die at a set time. In cancer cells, the DNA changes give different instructions. The changes tell the cancer cells to make many more cells quickly. Cancer cells can keep living when healthy cells die. This causes too many cells.

The cancer cells might form a mass called a tumor. The tumor can grow to invade and destroy healthy body tissue. In time, cancer cells can break away and spread to other parts of the body. When cancer spreads, it's called metastatic cancer.

### **Types of esophageal cancer**

Esophageal cancer is classified depending on the type of cells that are involved. The type of esophageal cancer you have helps determine your treatment options. Types of esophageal cancer include:

* **Adenocarcinoma.** Adenocarcinoma begins in the cells of the glands in the esophagus. These glands produce mucus. Adenocarcinoma happens most often in the lower part of the esophagus. Adenocarcinoma is the most common form of esophageal cancer in the United States. It affects mostly white men.
* **Squamous cell carcinoma.** Squamous cell carcinoma begins in the flat, thin cells that line the surface of the esophagus. Squamous cell carcinoma happens most often in the upper and middle parts of the esophagus. Squamous cell carcinoma is the most common esophageal cancer worldwide.
* **Other rare types.** Some rare forms of esophageal cancer include small cell carcinoma, sarcoma, lymphoma, melanoma and choriocarcinoma.

**Risk factors**

Risk factors for esophageal cancer include conditions and habits that cause irritation in the esophagus. Risk factors may include:

* A steady habit of drinking very hot liquids.
* Bile reflux.
* Difficulty swallowing because a muscle in the esophagus won't relax, a condition called achalasia.
* Drinking alcohol.
* Gastroesophageal reflux disease, also called GERD.
* Not eating enough fruits and vegetables.
* Obesity.
* Precancerous changes in the cells of the esophagus, called Barrett esophagus.
* Radiation treatment to the chest or upper abdomen.
* Smoking.

**Symptoms**

Esophageal cancer may not cause symptoms early on. Symptoms of esophageal cancer usually happen when the disease is advanced.

Signs and symptoms of esophageal cancer include:

* Difficulty swallowing.
* Chest pain, pressure or burning.
* Coughing or hoarseness.
* Weight loss without trying.
* Worsening indigestion or heartburn.

### 

### **When to see a doctor**

Make an appointment with your doctor or other healthcare professional if you have any symptoms that worry you.

**Complications**

As esophageal cancer advances, it can cause complications. Complications may include:

* **A blockage in the esophagus.** Cancer may make it difficult for food and liquid to pass through the esophagus.
* **Bleeding in the esophagus.** Esophageal cancer can cause bleeding. Though bleeding is usually gradual, it can be sudden and severe at times.
* **Pain.** Advanced esophageal cancer can cause pain.

**Prevention**

There's no sure way to prevent esophageal cancer, but you can reduce your risk if you:

### **Ask about esophageal cancer screening**

Screening for esophageal cancer may be an option for people with Barrett esophagus. Barrett esophagus is a precancerous condition caused by chronic acid reflux. It increases the risk of esophageal cancer.

If you have Barrett esophagus, ask your healthcare professional about screening. Screening typically involves exams to look at the inside of the esophagus for signs of cancer.

### **Drink alcohol in moderation, if at all**

If you choose to drink alcohol, do so in moderation. For healthy adults, that means up to one drink a day for women and up to two drinks a day for men.

### **Eat more fruits and vegetables**

Choose a healthy diet with a variety of fruits and vegetables. Food sources of vitamins and nutrients are best. Avoid taking large doses of vitamins in pill form, as they may be harmful.

### **Exercise most days of the week**

Aim for at least 30 minutes of exercise on most days of the week. If you haven't been active lately, ask your healthcare professional whether it's OK and start slowly.

### **Maintain a healthy weight**

If your weight is healthy, work to maintain that weight. If you need to lose weight, ask a healthcare professional about healthy ways to lower your weight. Eat fewer calories and slowly increase the amount of exercise.

### **Stop smoking**

Talk to your healthcare team about strategies and aids that can help you quit. Options include nicotine replacement products, medicines and support groups. If you've never smoked, don't start.

## **Diagnosis**

**Upper endoscopy**

Esophageal cancer diagnosis often begins with imaging tests to look at the esophagus. A thin, flexible tube with a camera may be passed down the throat to see the esophagus. A sample of tissue may be taken for lab testing.

### **Barium swallow study**

A barium swallow study is a test that uses X-rays to look at the digestive system. It can show changes in the esophagus, such as a growth that could be cancerous. Before the test, you drink a white liquid called barium. The barium coats your esophagus and makes it easier to see on X-rays. If anything worrying is found on the barium swallow study, your healthcare team might recommend having an endoscopy to check it out.

### **Upper endoscopy**

Upper endoscopy is a test to look at the upper digestive system. It uses a long, flexible tube with a camera at the end, called an endoscope, to see inside the body. To see inside the esophagus, a healthcare professional passes the endoscope down the throat and into the esophagus. The health professional looks for signs of cancer.

### **Biopsy**

A biopsy is a procedure to remove a sample of tissue for testing in a lab. To get the tissue sample, a healthcare professional passes special cutting tools through an endoscope. The health professional uses the tools to remove a very small amount of tissue from the inside of the esophagus. The tissue sample is sent to a lab to look for cancer cells.

### **Determining the extent of the cancer**

After an esophageal cancer diagnosis, you may have other tests to see if the cancer has spread. These tests help your healthcare team find out the extent of your cancer, called the stage. Cancer staging tests often involve imaging tests. The tests might look for signs of cancer in your lymph nodes or in other parts of your body. Your healthcare team uses the cancer staging test results to help create your treatment plan.

Imaging tests may include bronchoscopy, endoscopic ultrasound, CT, MRI and positron emission tomography scans, also called PET scans. Not every test is right for every person. Talk with your healthcare professional about which tests you will need.

The stages of esophageal cancer range from 0 to 4. A stage 0 esophageal cancer is small and only on the inside surface of the esophagus. As the cancer gets larger and grows deeper into the esophagus, the stages get higher. A stage 4 esophageal cancer has grown beyond the esophagus or has spread to the lymph nodes or other parts of the body.

**Treatment**

Treatment for small esophageal cancers usually begins with surgery to remove the cancer. If the cancer grows larger or spreads to other parts of the body, treatment might start with chemotherapy and radiation instead. Your healthcare team considers many factors when creating a treatment plan. These factors include your overall health, the type and stage of your cancer, and your preferences.

### **Surgery**

**Esophageal cancer surgery**

Surgery to remove the cancer can be used alone or in combination with other treatments.

Procedures used for esophageal cancer may include:

* **Removing the cancer from the inside of the esophagus.** Endoscopic resection is a procedure to remove the cancer and some of the healthy tissue around it. The procedure is done through a long, flexible tube, called an endoscope. The tube goes down the throat and into the esophagus. Special tools are passed through the endoscope to remove the cancer. This procedure might be an option if the cancer is very small and hasn't spread.
* **Removing the cancer and part of the esophagus.** Esophagectomy is surgery to remove part of the esophagus. During esophagectomy, the surgeon removes the part of the esophagus that contains the cancer and some nearby lymph nodes. The surgeon also may remove some of the upper part of the stomach. When the surgery involves removing some of the esophagus and some of the stomach it's called an esophagogastrectomy. The remaining esophagus is reconnected to the stomach. Usually this is done by pulling the stomach up to meet the remaining esophagus. If necessary, part of the colon is used to help join the two.

Esophageal cancer surgery carries a risk of serious complications. These complications may include infection and bleeding. There's also a risk of leakage from the area where the remaining esophagus is reattached to the stomach.

Surgery to remove the esophagus can be performed as an open procedure using large incisions. Surgery also may be done laparoscopically where special surgical tools are inserted through several small incisions in the skin. How your surgery is performed depends on your individual situation and how your surgeon wants to approach it.

### **Chemotherapy**

Chemotherapy treats cancer with strong medicines. Chemotherapy medicines are typically used before or after surgery in people with esophageal cancer. Chemotherapy can be combined with radiation therapy.

In people with advanced cancer that has spread beyond the esophagus, chemotherapy may be used alone to help relieve symptoms caused by the cancer.

Chemotherapy side effects depend on which medicines you receive. Common side effects include fatigue, nausea and vomiting, diarrhea, and loss of appetite.

### **Radiation therapy**

Radiation therapy treats cancer with powerful energy beams. The energy can come from X-rays, protons or other sources. For esophageal cancer, radiation therapy is most often done with a procedure called external beam radiation. During this treatment, you lie on a table while a machine moves around you. The machine directs radiation to precise points on your body. Radiation also can be placed inside your body near the cancer. This kind of radiation therapy, called brachytherapy, is less common.

Radiation therapy is often combined with chemotherapy in people with esophageal cancer. Radiation therapy also is used to relieve complications of advanced esophageal cancer. This may include treating a cancer that grows large enough to stop food from passing to your stomach.

Side effects of radiation to the esophagus include sunburn-like skin reactions, painful or difficult swallowing, and damage to nearby organs, such as the lungs and heart.

### **Combined chemotherapy and radiation**

Combining chemotherapy and radiation therapy may enhance the effectiveness of each treatment. Combined chemotherapy and radiation may be the only treatment you receive, or combined therapy can be used before surgery. But combining chemotherapy and radiation treatments increases the likelihood and severity of side effects.

### **Targeted drug therapy**

Targeted therapy for cancer is a treatment that uses medicines that attack specific chemicals in cancer cells. By blocking these chemicals, targeted treatments can cause cancer cells to die.

For esophageal cancer, targeted therapy may be combined with chemotherapy for advanced cancers that can't be removed with surgery or for cancers that come back after treatment.

Some targeted therapies only work in people whose cancer cells have certain DNA changes. Your cancer cells may be tested in a lab to see if these medicines might help you.

### **Immunotherapy**

Immunotherapy for cancer is a treatment with medicine that helps the body's immune system kill cancer cells. The immune system fights off diseases by attacking germs and other cells that shouldn't be in the body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells.

For esophageal cancer, immunotherapy is sometimes used before or after surgery. It also may be used for advanced cancers that can't be removed with surgery or for cancers that come back after treatment.

### **Treatments for complications**

**Esophageal stent**

Esophageal cancer sometimes grows large enough to narrow the esophagus. It can cause difficulty swallowing. Treatments for this complication can include:

* **Relieving esophageal obstruction.** If your esophageal cancer has narrowed your esophagus, a surgeon may use an endoscope and special tools to place a metal tube called a stent. The stent holds the esophagus open. Other options include surgery, radiation therapy, chemotherapy, laser therapy and photodynamic therapy.
* **Providing nutrition.** Your healthcare professional may recommend a feeding tube if you're having trouble swallowing or if you're having esophagus surgery. A feeding tube allows nutrition to be delivered directly to your stomach or small intestine. This gives your esophagus time to heal after cancer treatment.

### **Palliative care**

Palliative care is a special type of healthcare that helps you feel better when you have a serious illness. If you have cancer, palliative care can help relieve pain and other symptoms. A healthcare team that may include doctors, nurses and other specially trained health professionals provides palliative care. The care team's goal is to improve quality of life for you and your family.

Palliative care specialists work with you, your family and your care team. They provide an extra layer of support while you have cancer treatment. You can have palliative care at the same time you're getting strong cancer treatments, such as surgery, chemotherapy or radiation therapy.

The use of palliative care with other proper treatments can help people with cancer feel better and live longer.

**Alternative medicine**

Complementary and alternative esophageal cancer treatments can't cure esophageal cancer. But these treatments can be combined with your healthcare team's care to help relieve pain and other symptoms.

Options may include:

* Acupuncture.
* Guided imagery.
* Hypnosis.
* Massage.
* Relaxation techniques.

Ask your healthcare team whether these options are safe for you.

## **Diagnostic Considerations**

Esophageal lesions other than cancer that can cause dysphagia include the following:

* Achalasia
* Esophageal stricture from gastroesophageal reflux
* Benign esophageal tumors (principally esophageal leiomyoma)

Achalasia may be clinically indistinguishable from esophageal cancer. Patients present with a long history of regurgitation and slowly progressive dysphagia. Upper gastrointestinal imaging (eg, barium study) shows a typical "bird's beak" filling defect.

Caution is required to differentiate achalasia from so-called pseudoachalasia, which can mimic this benign condition; it is crucial therefore to follow up with endoscopy for mucosal assessment and biopsy to rule out any malignant pathology. Esophagogastroduodenoscopy (EGD) has low sensitivity for the diagnosis of achalasia; results are often reported as normal in early achalasia. Esophageal manometry confirms the diagnosis by showing incomplete relaxation (increased resting pressure/tone) of the lower esophageal sphincter (LES)

Esophageal stricture is characterized by slowly progressive dysphagia and heartburn. EGD confirms the diagnosis.

In patients with HIV infection or AIDS, consider an underlying esophageal lymphoma in a clinical presentation consistent with infectious esophagitis that is not responsive to adequate therapy. This is especially true when esophageal ulcerations are present. Recognition of primary esophageal lymphoma is challenging. primary oesophageal lymphoma is particularly challenging because of its rarity, diverse clinical presentations, and nonspecific radiologic and endoscopic features; the tumor maybe located predominantly in the submucosa, which complicates. standard diagnostic approaches.

## **Differential Diagnoses**

* Achalasia
* Esophageal Leiomyoma
* Esophageal Stricture
* Gastric Cancer

## 

## **Epidemiology**

### United States statistics

The American Cancer Society estimates that 22,070 new cases of esophageal cancer (17,430 in men and 4640 in women) will be diagnosed in the United States in 2025, and that 16,1250 persons (12,940 men and 3310 women) will die of the disease.Esophageal cancer is the 17th most common cancer in the US, but the seventh most common cause of cancer death in males.The 5-year survival rate from 2014 to 2020 was 21.6%.

The incidence of esophageal carcinoma is approximately 3-6 cases per 100,000 population, although certain endemic areas appear to have higher per-capita rates. The age-adjusted annual incidence was 4.2 per 100,000 men and women, based on 2017-2021 cases.

The epidemiology of esophageal carcinoma has changed markedly over the past several decades in the United States.Until the 1970s, squamous cell carcinoma was the most common type of esophageal cancer (90-95%). It was typically located in the thoracic esophagus and most frequently affected African-American men with a long history of smoking and alcohol consumption.

Subsequently, rates of esophageal adenocarcinoma rose markedly, particularly in Whites. In White men, the incidence rate of esophageal adenocarcinoma exceeded that of squamous cell carcinoma around 1990, while in White women aged 45–59 years, adenocarcinoma overtook squamous cell carcinoma in 2006–2010.

From 1973 to 1996, the incidence of esophageal adenocarcinoma increased by 8.2% annually. From 1996 to 2006, the rate of increase fell to 1.3% annually, principally because of a plateau in the incidence of early-stage disease. Prior to 1996, early-stage cases increased by 10% annually; subsequently, they declined by 1.6% annually.From 2004 to 2014, incidence rates of esophageal adenocarcinoma in the United States fell on average 1.4% each year.

### International statistics

Esophageal câncer is the 11th most common cancer and the 7th most common cause of cancer deaths worldwide. It is endemic in many parts of the world, particularly in the third world countries, where it is the fourth most common cause of cancer deaths. Incidence rates are variable worldwide, with the highest rates found in eastern Asia and southern and eastern Africa, and the lowest rates in western and northern Africa and Central America in both men and women.

In some regions, such as areas of northern Iran, some areas of southern Russia, and northern China (sometimes called an "esophageal cancer belt"), the incidence of esophageal carcinoma may be as high as 800 cases per 100,000 population. Major risk factors in these areas are not well known but are probably related to the poor nutritional status, including low intake of fruits and vegetables and drinking very hot beverages. Unlike in the United States, squamous cell carcinoma is responsible for 95% of all esophageal cancers worldwide.

### Sex- and age-related demographics

Esophageal cancer is more common in men than in women. Worldwide, esophageal cancer is 2 to 3 times more common in men; in the US, it is more than 4 times more common in men.

Esophageal cancer occurs most commonly during the sixth and seventh decades of life. The disease becomes more common with advancing age; it is about 20 times more common in persons older than 65 years than it is in individuals below that age. Median age at diagnosis is 68 years.

**STAGING**

TNM staging is as follows:

* Tis - High-grade dysplasia (malignant cells confined to the epithelium by the basement membrane)
* T1 - Tumor invades the lamina propria, muscularis mucosae, or submucosa
* T1a - Tumor invades the lamina propria or muscularis mucosae
* T1b - Tumor invades the submucosa
* T2 - Tumor invades the muscularis propria
* T3 - Tumor invades adventitia
* T4 - Tumor invades adjacent structures
* T4a -Tumor invading into pleura, pericardium, azygos vein, diaphragm, or peritoneum
* T4b - Tumor invading other adjacent structures (eg, aorta, vertebral body, trachea)
* N0 - No regional lymph node metastasis
* N1 - 1-2 regional lymph nodes (N1 is site dependent)
* N2 - 3-6 regional lymph nodes
* N3 - More than 6 regional lymph nodes
* M0 - No distant metastasis
* M1 - Distant metastasis

Clinical Staging Classification (Squamous Cell Carcinoma)

| Stage 0 | Tis | N0 | M0 |
| --- | --- | --- | --- |
| Stage I | T1 | N0-1 | M0 |
| Stage II | T2 | N0 | M0 |
|  | T3 | N0 | M0 |
| Stage III | T3 | N1 | M0 |
|  | T1-3 | N2 | M0 |
| Stage IVA | T4 | N0-2 | M0 |
|  | Any T | N3 | M0 |
| Stage IVB | Any T | Any N | M1 |

Table 4. Clinical Staging Classification (Adenocarcinoma)

| Stage 0 | Tis | N0 | M0 |
| --- | --- | --- | --- |
| Stage I | T1 | N0 | M0 |
| Stage IIA | T1 | N1 | M0 |
| Stage IIB | T2 | N0 | M0 |
| Stage III | T2 | N1 | M0 |
|  | T3 | N0-1 | M0 |
|  | T4a | N0-1 | M0 |
| Stage IVA | T1-4a | N2 | M0 |
|  | T4b | N0-2 | M0 |
|  | Any T | N3 | M0 |
| Stage IVB | Any T | Any N | M1 |

All esophageal tumors, as well as tumors with epicenters within 5 cm of the esophagogastric junction that also extend into the esophagus, are classified and staged according to the AJCC/UICC esophageal scheme. Tumors with an epicenter in the stomach that are more than 5 cm from the esophagogastric junction or those within 5 cm of the esophagogastric junction without extension into the esophagus are staged using the gastric carcinoma scheme.

However, this classification may not work well for patients who have received preoperative therapy. Some other shortcomings associated with the current staging classification are as follows:

* Inclusion of proximal 5 cm of the stomach
* Lack of guidance for regional resectable and unresectable cancer
* Emphasis on the number of nodes rather than their size and anatomic locations/significance.

Other classifications—such as that of the Japanese Society for Esophageal Diseases, which is widely used in Asia—differ from that of the AJCC/UICC, especially regarding lymph node distribution and nomenclature.

## 

## **Antineoplastics, Antimetabolite**

## 

These agents inhibit cell growth and proliferation. They interfere with DNA synthesis by blocking the methylation of deoxyuridylic acid.

## Fluorouracil (Adrucil)

Fluorouracil is a pyrimidine antimetabolite. Several mechanisms of action have been proposed, including inhibition of thymidylate synthase and inhibition of RNA synthesis. This agent is also a potent radiosensitizer.

## Capecitabine (Xeloda)

Capecitabine is a pyrimidine antimetabolite and a prodrug of fluorouracil. It forms the active moiety, fluorouracil, by undergoing hydrolysis in the liver and tissues. Capecitabine is used off-label for the treatment of esophageal cancer.

## **Antineoplastics, Alkylating**

## 

These agents inhibit cell growth and proliferation, interfering with DNA synthesis by the formation of DNA cross-links. Alkylating agents can have serious adverse effects such as bone marrow suppression, anaphylactic-like reactions, ototoxicity, renal toxicity, and vomiting.

## Cisplatin

Intrastrand cross-linking of DNA and inhibition of DNA precursors are among the proposed mechanisms of action for cisplatin. This agent is used in combination with radiation therapy. Cisplatin has black box warnings for adverse reactions, including anaphylactic-like reactions, ototoxicity, and renal toxicity.

## Carboplatin

Carboplatin is a platinum alkylating agent that interferes with the function of DNA by producing interstrand DNA cross-links. It can be used in combination with paclitaxel for the treatment of esophageal cancer, which is an off-label indication. Carboplatin has black box warnings including bone marrow suppression, anaphylactic reactions, and vomiting.

## Oxaliplatin (Eloxatin (DSC))

Oxaliplatin is a platinum alkylating agent that inhibits DNA replication and transcription, resulting in cell death. It can be used in combination chemotherapy for the treatment of esophageal cancer, which is an off-label indication. It has a black box warning for anaphylactic reactions, which can be managed with epinephrine, corticosteroids, and antihistamines.

## **PD-1/PD-L1 Inhibitors**

## 

PD-1 and related target PD-ligand 1 (PD-L1) are expressed on the surface of activated T cells under normal conditions. PD-L1/PD-1 interaction inhibits immune activation and reduces T-cell cytotoxic activity when bound.

## Nivolumab (Opdivo)

Indicated in combination with fluoropyrimidine- and platinum-containing chemotherapy as first-line treatment for advanced or metastatic esophageal or gastroesophageal junction adenocarcinoma or esophageal squamous cell carcinoma that is PD-L1 positive (≥1%). Indicated as second-line monotherapy for unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma in patients previously treated with fluoropyrimidine- and platinum-based chemotherapy. Finally, indicated for completely resected esophageal or gastroesophageal junction cancer in patients with residual pathologic disease who have received neoadjuvant chemoradiotherapy.

## Nivolumab/hyaluronidase (Nivolumab/hyaluronidase-nvhy, Opdivo Qvantig)

Formulation of nivolumab with hyaluronidase, which enables subcutaneous administration.

## Tislelizumab (Tevimbra)

Indicated, in combination with platinum-containing chemotherapy, for the first-line treatment of unresectable or metastatic esophageal squamous cell carcinoma that expresses PD-L1; in combination with platinum- and fluoropyrimidine-based chemotherapy, for the the first-line treatment of unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma that expresses PD-L1; and as a single agent for second-line treatment of unresectable or metastatic esophageal squamous cell carcinoma, after prior systemic chemotherapy that did not include a PD-L1 inhibitor.

## Pembrolizumab (Keytruda)

Indicated in combination with platinum- and fluoropyrimidine-based chemotherapy in esophageal tumors that express PD-L1 with CPS ≥1; as single-agent second-line therapy in esophageal squamous cell cancer that expresses PD-L1 with CPS ≥10; and in combination with chemotherapy in esophageal and gastroesophageal junction adenocarcinoma that expresses PD-L1 with CPS ≥1

## **Antineoplastics, Anti microtubular**

## 

These agents prevent cell growth and proliferation. They work by enhancing tubulin dimers, stabilizing existing microtubules, and inhibiting microtubule disassembly.

## Docetaxel (Beizray, Docefrez, Docivyx)

Docetaxel inhibits the depolymerization of tubulin, which inhibits DNA, RNA, and protein synthesis. It can be used in combination with cisplatin and fluorouracil for the treatment of esophageal cancer, which is an off-label indication. It has several black box warnings such as bone marrow suppression, fluid retention, and hypersensitivity reactions.

Use of docetaxel is not recommended in certain patients with hepatic impairment. Patients receiving treatment with docetaxel should be premedicated with corticosteroids the day before administration to help reduce fluid retention and hypersensitivity reactions.

## Paclitaxel (Taxol)

Paclitaxel promotes microtubule assembly, interferes with the G2 mitotic phase, and inhibits cell replication. Although not FDA approved, it has been used in combination chemotherapy for the treatment of esophageal cancer. Paclitaxel has an orphan drug indication for the treatment of adenocarcinoma. Black box warnings for this drug include bone marrow suppression and hypersensitivity reactions.

## **Antineoplastics, Anthracycline**

Anthracycline antineoplastics inhibit DNA and RNA synthesis by steric obstruction. They intercalate between DNA base pairs and trigger DNA cleavage by topoisomerase II.

## Epirubicin (Ellence, Pharmorubicin)

Epirubicin inhibits DNA and RNA synthesis. It can be used off label as part of a combination chemotherapy regimen for the treatment of esophageal cancer. It has several black box warnings, including bone marrow suppression, extravasation, myocardial toxicity, and secondary malignancy. Dosage reduction is recommended in patients with mild to moderate hepatic impairment.

## **Antineoplastics, Topoisomerase Inhibitors**

## 

These agents prevent cell growth and proliferation. They work by binding to topoisomerase and causing single-strand DNA breaks.

## Irinotecan (Camptosar)

Irinotecan binds reversibly to the topoisomerase I–DNA complex and prevents the ligation of the cleaved DNA strand. It can be used as part of combination chemotherapy for the treatment of esophageal cancer, which is an off-label indication. Black box warnings for irinotecan include bone marrow suppression and diarrhea.

## **Thymidine Analog**

## 

Following uptake into cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis and inhibits cell proliferation.

## Tipiracil/trifluridine (Lonsurf)

Tipiracil is a thymidine phosphorylase inhibitor that increases trifluridine exposure by inhibiting its metabolism. Trifluridine is a thymidine-based nucleoside analog that incorporates into DNA, interferes with DNA synthesis, and inhibits cell proliferation. It is indicated for metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma previously treated with at least 2 prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

## **Antineoplastics, Other**

## 

This category includes miscellaneous antineoplastic agents that cause cytotoxic activity by various mechanisms of action.

## Porfimer (Photofrin)

Porfimer is a photodynamic therapy that causes cytotoxic activity by producing oxygen free-radicals in the presence of laser light. It also can release thromboxane A2, leading to necrosis and vascular occlusion. It is indicated for palliation in patients with partially or completely obstructing esophageal cancer.

## Antineoplastics, Anti-HER2

## Trastuzumab (Herceptin, Herzuma, Kanjinti)

Monoclonal antibody, inhibits growth of tumor cells that overexpress HER2

## Antineoplastics, VEGF Inhibitors

## Ramucirumab (Cyramza)

Vascular endothelial growth factor receptor 2 (VEGFR2) antagonist. Indicated for use as a single agent or in combination with paclitaxel for advanced gastro-esophageal junction adenocarcinoma in patients with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

## Anti-Claudin Monoclonal Antibodies

## Zolbetuximab (Vyloy, Zolbetuximab-clzb)

Indicated in combination with fluoropyrimidine- and platinum-containing chemotherapy for first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma in patients with claudin (CLDN) 18.2-positive tumors,

## Antineoplastics, Monoclonal Antibody

## Ipilimumab (Yervoy)

Recombinant, human cytotoxic T-lymphocyte antigen 4 (CTLA-4) - blocking antibody. Indicated in combination with nivolumab for first-line treatment of patients with unresectable advanced or metastatic esophageal squamous cell carcinoma whose tumors express PD-L1 (≥1%)

## **Outlook / Prognosis**

That depends on factors like your overall health and if you received a diagnosis before the tumor spread. Healthcare providers often successfully treat early-stage esophageal cancer. About 46% of people treated for early-stage esophageal cancer are alive five years after diagnosis.

Healthcare providers may not be able to destroy the cancer, especially if it’s already spread. They can provide treatment to help you live well as long as you’re able, maintain quality of life and ease symptoms. They may recommend palliative care that can help you live comfortably and without pain.

## **Living With**

Esophageal cancer surgery may have significant side effects like nausea and vomiting or heartburn. You may need help to manage these side effects. Many people treated for esophageal cancer have the following issues:

* Difficulty eating: Esophageal cancer makes you lose weight because you can’t swallow food or it hurts to swallow food. Treatment may remove the cancer, but you still may have trouble swallowing. If that’s your situation, ask your healthcare provider for suggestions such as eating smaller meals or drinking nutritional supplements.
* Dumping syndrome: This happens when your stomach takes the place of your esophagus. Your stomach may not be able to hold food for digestion so food passes too quickly into your intestines. Dumping syndrome symptoms may include nausea, vomiting, diarrhea, stomach cramps, sweating or flushing of the skin.

#### **Yes, it can come back. You can reduce that risk by:**

* Limiting alcohol: Frequently drinking a lot of alcohol increases your risk that esophageal cancer will come back.
* Avoiding tobacco: Tobacco use is another risk factor for esophageal cancer returning. If you smoke, please try to stop. Ask your healthcare provider if you want help to stop smoking.

**COMMON QUESTIONS AND ANSWER SET**

## What kind of esophageal cancer do I have?

The vast majority of esophageal cancers are either adenocarcinoma or squamous cell carcinoma. Adenocarcinoma usually starts in the mucus-secreting glandular cells in the lower part of the esophagus, often linked to conditions like GERD and Barrett's esophagus. Squamous cell carcinoma starts in the flat cells lining the upper and middle parts of the esophagus and is more common in certain populations and regions. Your doctor will determine the exact type based on a biopsy of the tumor.

## What stage is my cancer?

Staging uses the TNM system, which looks at how deeply the tumor has invaded the esophagus wall (T), whether lymph nodes are involved (N), and whether the cancer has spread to other organs (M). Stages range from I (early, localized) to IV (advanced/metastatic). The stage is determined by imaging studies, endoscopy, and sometimes surgical exploration, and it guides treatment and prognosis.

## What treatments do you recommend?

Treatment depends on the cancer type, stage, and your overall health:

* Early-stage (localized): Surgery (esophagectomy) is often recommended, sometimes with chemotherapy or chemoradiation before or after surgery.
* Locally advanced: A combination of chemotherapy and radiation (chemoradiation), with or without surgery.
* Advanced/metastatic: Chemotherapy, targeted therapies, immunotherapy, and palliative treatments to control symptoms and improve quality of life.

## Is there a cure?

Some patients with early-stage esophageal cancer can be cured, especially if the tumor can be completely removed with surgery. For more advanced stages, cure is less likely, but treatment can often control the disease, relieve symptoms, and extend life.

## If there isn’t a cure, what can you do to help me?

If cure is not possible, the focus shifts to palliative care—controlling symptoms (such as difficulty swallowing or pain), improving quality of life, and supporting you and your family. Treatments may include palliative chemotherapy, radiation, endoscopic procedures (like stenting), and comprehensive supportive care.

## How long can I live with this cancer?

Survival depends on the stage at diagnosis, cancer type, and response to treatment. Early-stage cancers have a better prognosis, while advanced cancers are more challenging to treat. Your doctor can provide more specific information based on your individual case and test results.

## Do I need any genetic or biomarker testing done?

Yes. Current guidelines recommend testing for biomarkers such as HER2, PD-L1, and mismatch repair (MMR)/microsatellite instability (MSI) status in all newly diagnosed esophageal cancers. These results can help guide targeted therapy and immunotherapy options and may affect your treatment plan.

## **Genomic Alterations in Esophageal Cancer**

## Esophageal Squamous Cell Carcinoma (ESCC)

* Most Frequently Mutated Genes:
  + TP53: The most commonly mutated gene in ESCC, with mutation rates as high as 80–97%. These mutations are central to tumorigenesis.
  + NOTCH1: Frequently mutated, involved in cell differentiation and signaling.
  + EP300: Mutated in a significant subset, affecting chromatin remodeling and gene expression.
  + KMT2C, CSMD3, FAM135B: Other recurrently mutated genes.
  + ARID1A, CDKN2A: Higher mutation rates and frequent copy number alterations, contributing to cell cycle dysregulation and chromatin remodeling.
* Copy Number Alterations:
  + Amplifications: CCND1, FGF3, FGF4, FGF19 gene cluster (notably on 11q13.3), NKX2-1, MYC.
  + Deletions: CDKN2A/B, RB1, ATM, ATR.
* Pathways Involved:
  + Cell cycle regulation, chromatin modification, Notch, and JAK-STAT signaling pathways are commonly affected.
* Mutational Signatures:
  + Signatures associated with APOBEC enzyme activity, DNA repair defects, and environmental exposures (e.g., tobacco, alcohol).
* Tumor Mutation Burden (TMB) and PD-L1:
  + A subset of ESCC cases show high TMB and PD-L1 expression, which may predict response to immunotherapy

## **Doctor-Patient Conversation: Esophageal Cancer**

Doctor: Thank you for coming in today. I have your test results, and I’d like to discuss them with you. The diagnosis is esophageal cancer.

Patient: That’s difficult news. What kind of esophageal cancer do I have?

Doctor: There are two main types: adenocarcinoma and squamous cell carcinoma. Your biopsy shows you have [adenocarcinoma/squamous cell carcinoma]. This information helps us choose the best treatment for you.

Patient: What stage is my cancer?

Doctor: We use imaging tests, endoscopy, and sometimes surgical exploration to determine the stage. The stage tells us how far the cancer has grown and whether it has spread to lymph nodes or other organs. Your cancer is stage [I/II/III/IV], which means [brief explanation tailored to stage].

Patient: What are my treatment options?

Doctor: Treatment depends on the stage and your overall health. For early-stage disease, surgery may be recommended, sometimes with chemotherapy or radiation before or after. For more advanced cases, we may use chemotherapy, radiation, targeted therapy, or immunotherapy. If the cancer can’t be cured, our focus will be on controlling symptoms and maintaining your quality of life.

Patient: Is there a cure?

Doctor: Some early-stage esophageal cancers can be cured, especially if we can remove the tumor completely. For more advanced cases, cure is less likely, but treatment can often control the disease and help you feel better for longer.

Patient: If there isn’t a cure, what can you do to help me?

Doctor: We can offer palliative treatments to relieve symptoms like difficulty swallowing or pain. This may include palliative radiation, stenting, or medications. We’ll also provide supportive care and connect you with palliative care specialists to help with symptoms and emotional support.

Patient: How long can I live with this cancer?

Doctor: Survival depends on the stage, type, and your response to treatment. Early-stage cancers have a better outlook, while advanced cancers are more challenging. We’ll discuss your individual situation in detail and support you throughout.

Patient: Do I need any genetic or biomarker testing?

Doctor: Yes. We recommend testing your tumor for HER2, PD-L1, and mismatch repair (MMR) status. These results help us decide if targeted therapy or immunotherapy may be options for you.

Patient: What should I do next?

Doctor: Bring a family member or friend to appointments for support, write down your questions, and keep copies of your test results. Our care team will help you organize your care and provide resources for nutrition, emotional support, and symptom management

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**CERVICAL CANCER**

**DEFINITION AND DESCRIPTION**

Cervical cancer is a growth of cells that starts in the cervix. The cervix is the lower part of the uterus that connects to the vagina.

Various strains of the human papillomavirus, also called HPV, play a role in causing most cervical cancers. HPV is a common infection that's passed through sexual contact. When exposed to HPV, the body's immune system typically prevents the virus from doing harm. In a small percentage of people, however, the virus survives for years. This contributes to the process that causes some cervical cells to become cancer cells.

You can reduce your risk of developing cervical cancer by having screening tests and receiving a vaccine that protects against HPV infection.

When cervical cancer happens, it's often first treated with surgery to remove the cancer. Other treatments may include medicines to kill the cancer cells. Options might include chemotherapy and targeted therapy medicines. Radiation therapy with powerful energy beams also may be used. Sometimes treatment combines radiation with low-dose chemotherapy.

**Causes**

**Where cervical cancer begins**

Cervical cancer begins when healthy cells in the cervix develop changes in their DNA. A cell's DNA contains the instructions that tell a cell what to do. The changes tell the cells to multiply quickly. The cells continue living when healthy cells would die as part of their natural life cycle. This causes too many cells. The cells might form a mass called a tumor. The cells can invade and destroy healthy body tissue. In time, the cells can break away and spread to other parts of the body.

Most cervical cancers are caused by HPV. HPV is a common virus that's passed through sexual contact. For most people, the virus never causes problems. It usually goes away on its own. For some, though, the virus can cause changes in the cells that may lead to cancer.

### **Types of cervical cancer**

Cervical cancer is divided into types based on the type of cell in which the cancer begins. The main types of cervical cancer are:

* **Squamous cell carcinoma.** This type of cervical cancer begins in thin, flat cells, called squamous cells. The squamous cells line the outer part of the cervix. Most cervical cancers are squamous cell carcinomas.
* **Adenocarcinoma.** This type of cervical cancer begins in the column-shaped gland cells that line the cervical canal.

Sometimes, both types of cells are involved in cervical cancer. Very rarely, cancer occurs in other cells in the cervix.

**Risk factors**

Risk factors for cervical cancer include:

* **Smoking tobacco.** Smoking increases the risk of cervical cancer. When HPV infections happen in people who smoke, the infections tend to last longer and are less likely to go away. HPV causes most cervical cancers.
* **Increasing number of sexual partners.** The greater your number of sexual partners, and the greater your partner's number of sexual partners, the greater your chance of getting HPV.
* **Early sexual activity.** Having sex at an early age increases your risk of HPV.
* **Other sexually transmitted infections.** Having other sexually transmitted infections, also called STIs, increases the risk of HPV, which can lead to cervical cancer. Other STIs that increase the risk include herpes, chlamydia, gonorrhea, syphilis and HIV/AIDS.
* **A weakened immune system.** You may be more likely to develop cervical cancer if your immune system is weakened by another health condition and you have HPV.
* **Exposure to miscarriage prevention medicine.** If your parents took a medicine called diethylstilbestrol, also known as DES, while pregnant, your risk of cervical cancer might be increased. This medicine was used in the 1950s to prevent miscarriage. It's linked to a type of cervical cancer called clear cell adenocarcinoma.

**Prevention**

To reduce your risk of cervical cancer:

* **Ask your doctor about the HPV vaccine.** Receiving a vaccination to prevent HPV infection may reduce your risk of cervical cancer and other HPV-related cancers. Ask your health care team if an HPV vaccine is right for you.
* **Have routine Pap tests.** Pap tests can detect precancerous conditions of the cervix. These conditions can be monitored or treated in order to prevent cervical cancer. Most medical organizations suggest beginning routine Pap tests at age 21 and repeating them every few years.
* **Practice safe sex.** Reduce your risk of cervical cancer by taking measures to prevent sexually transmitted infections. This may include using a condom every time you have sex and limiting the number of sexual partners you have.
* **Don't smoke.** If you don't smoke, don't start. If you do smoke, talk to a healthcare professional about ways to help you quit.

### **Screening**

**Pap test**

Screening tests can help detect cervical cancer and precancerous cells that may one day develop into cervical cancer. Most medical organizations suggest beginning screening for cervical cancer and precancerous changes at age 21. The tests are usually repeated every few years.

Screening tests include:

* **Pap test.** During a Pap test, a member of your health care team scrapes and brushes cells from your cervix. The cells are then examined in a lab to check for cells that look different.  
  A Pap test can detect cancer cells in the cervix. It also can detect cells that have changes that increase the risk of cervical cancer. These are sometimes called precancerous cells.
* **HPV DNA test.** The HPV DNA test involves testing cells from the cervix for infection with any of the types of HPV that are most likely to lead to cervical cancer.

Discuss your cervical cancer screening options with your health care team.

### **Diagnosis**

**Cone biopsy**

If you might have cervical cancer, testing is likely to start with a thorough exam of your cervix. A special magnifying instrument, called a colposcope, is used to check for signs of cancer.

During the colposcopic exam, a doctor removes a sample of cervical cells for lab testing. To get the sample, you might need:

* **Punch biopsy,** which uses a sharp tool to pinch off small samples of cervical tissue.
* **Endocervical curettage,** which uses a small, spoon-shaped instrument, called a curet, or a thin brush to scrape a tissue sample from the cervix.

If the results of these tests are concerning, you might have more tests. These might include:

* **Electrical wire loop,** which uses a thin, low-voltage electrified wire to take a small tissue sample. Generally, this is done in a doctor's office. You receive medicine to numb the area to lessen any discomfort during the procedure. This test also may be called a loop electrosurgical excision procedure, also known as LEEP.
* **Cone biopsy**, also called conization, is a procedure that allows your doctor to take deeper layers of cervical cells for testing. A cone biopsy is often done in a hospital. You may receive medicine to put you in a sleep-like state so that you won't be aware during the procedure.

### **Staging**

If you're diagnosed with cervical cancer, you might need other tests to find out the extent of the cancer, also called the stage. Your health care team uses the information from staging tests to plan your treatment.

Tests used for cervical cancer staging include:

* **Imaging tests.** Imaging tests make pictures of the body. They can show the location and size of the cancer. Tests might include X-ray, MRI, CT and positron emission tomography (PET) scan.
* **Visual examination of your bladder and rectum.** Your doctor may use special scopes to look for signs of cancer inside your bladder and rectum.

The stages of vaginal cancer range from 1 to 4. The lowest number means that the cancer is only in the cervix. As the numbers get higher, the cancer is more advanced. A stage 4 cervical cancer may have grown to involve nearby organs or spread to other areas of the body.

**Treatment**

Treatment for cervical cancer depends on several factors, such as the stage of the cancer, other health conditions you may have and your preferences. Surgery, radiation, chemotherapy or a combination of the three may be used.

### **Surgery**

Small cervical cancers that haven't grown beyond the cervix are typically treated with surgery. The size of your cancer, its stage and whether you would like to consider becoming pregnant in the future will determine which operation is best for you.

Options might include:

* **Surgery to cut away the cancer only.** For a very small cervical cancer, it might be possible to remove all the cancer with a cone biopsy. This procedure involves cutting away a cone-shaped piece of cervical tissue and leaving the rest of the cervix intact. This option may make it possible for you to consider becoming pregnant in the future.
* **Surgery to remove the cervix, called a trachelectomy.** A small cervical cancer might be treated with a radical trachelectomy procedure. This procedure removes the cervix and some surrounding tissue. The uterus remains after this procedure, so it may be possible to become pregnant, if you choose.
* **Surgery to remove the cervix and uterus, called a hysterectomy.** Most cervical cancers that have not spread beyond the cervix are treated with a radical hysterectomy operation. This involves removing the cervix, uterus, part of the vagina and nearby lymph nodes. A hysterectomy can often cure the cancer and stop it from coming back. But removing the uterus makes it impossible to become pregnant.

Minimally invasive hysterectomy may be an option for very small cervical cancers that have not spread, known as microinvasive cancers. This procedure involves making several small cuts in the abdomen rather than one large cut. People who have minimally invasive surgery tend to recover faster and spend less time in the hospital. But some research has found that minimally invasive hysterectomy may be less effective than traditional hysterectomy. If you're considering minimally invasive surgery, discuss the benefits and risks of this approach with your surgeon.

### **Radiation therapy**

Radiation therapy uses powerful energy beams to kill cancer cells. The energy can come from X-rays, protons or other sources. Radiation therapy is often combined with chemotherapy as the primary treatment for cervical cancers that have grown beyond the cervix. It also can be used after surgery if there's an increased risk that the cancer will come back.

Radiation therapy can be given:

* Externally, called external beam radiation therapy. A radiation beam is directed at the affected area of the body.
* Internally, it is called brachytherapy. A device filled with radioactive material is placed inside your vagina, usually for only a few minutes.
* Both externally and internally.

If you haven't started menopause, radiation therapy might cause menopause. Ask your health care team about ways to preserve your eggs before treatment.

### **Chemotherapy**

Chemotherapy uses strong medicines to kill cancer cells. For cervical cancer that has spread beyond the cervix, low doses of chemotherapy are often combined with radiation therapy. This is because chemotherapy may enhance the effects of the radiation. Higher doses of chemotherapy might be recommended to help control symptoms of very advanced cancer. Chemotherapy may be used before surgery to reduce the size of the cancer.

### **Targeted therapy**

Targeted therapy uses medicines that attack specific chemicals in the cancer cells. By blocking these chemicals, targeted treatments can cause cancer cells to die. Targeted therapy is usually combined with chemotherapy. It might be an option for advanced cervical cancer.

### **Immunotherapy**

Immunotherapy is a treatment with medicine that helps your immune system kill cancer cells. Your immune system fights off diseases by attacking germs and other cells that shouldn't be in your body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells. For cervical cancer, immunotherapy might be considered when the cancer is advanced and other treatments aren't working.

### **Palliative care**

Palliative care is a special type of health care that helps you feel better when you have a serious illness. If you have cancer, palliative care can help relieve pain and other symptoms. A team that can include doctors, nurses and other specially trained professionals provides palliative care. The team's goal is to improve quality of life for you and your family.

Palliative care specialists work with you, your family and your care team to help you feel better. They provide an extra layer of support while you have cancer treatment. You can have palliative care at the same time as strong cancer treatments, such as surgery, chemotherapy or radiation therapy.

Using palliative care along with all the other appropriate treatments can help people with cancer feel better and live longer

## **Diagnostic Considerations**

In addition to the conditions listed in the differential diagnosis, other disorders to consider in a woman with possible cervical cancer include the following:

* Cervicitis/infection, particularly granulomatous (which is rare)
* Primary melanoma and Paget disease
* Vaginal cancer

Another rare possibility is that a primary cancer elsewhere in the body has metastasized to the cervix.

## **Differential Diagnoses**

* Cervicitis
* Endometrial Carcinoma
* Pelvic Inflammatory Disease
* Vaginitis

## 

## **Epidemiology**

Cervical cancer is the third most common malignancy in women worldwide. The frequency varies considerably between developed and developing countries, however: Cervical cancer is the second most common cancer in developing countries, but only the tenth most common in developed countries. Similarly, cervical cancer is the second most common cause of cancer-related deaths in women in developing countries but is not even among the top 10 causes in developed countries.

In the United States, cervical cancer is relatively uncommon. The incidence of invasive cervical cancer has declined steadily in the United States over the past few decades; for example, since 2004, rates have decreased by 2.1% per year in women younger than 50 years and by 3.1% per year in women 50 years of age and older.This trend has been attributed to mass screening with Pap tests.Cervical cancer rates continue to rise in many developing countries, however.

A study of US cancer registry data showed that rates of cervical cancer among young women (aged 15-29 years) decreased from 1999 to 2017. The greatest declines were observed among those aged 15 to 20 years, which may be attributable to HPV vaccination.

The American Cancer Society (ACS) estimated that in the United States, 13,820 new cases of cervical cancer would be diagnosed in 2024.Internationally, more than 500,000 new cases are diagnosed each year; rates vary widely, ranging from an annual incidence of 4.5 cases per 100,000 in Western Asia to 34.5 per 100,000 women in Eastern Africa.In industrialized countries with well-established cytology screening programs, the incidence of cervical cancer ranges from 4 to 10 per 100,000 women.

The incidence of CIN 2/3 disease in the US is about 150 per 100,000 women, with the peak incidence around 800 per 100,000 women in the 25-29 year age group. The incidence of abnormal cytology screens for all ages is an order of magnitude larger, at 7800 per 100,000 women.

Forouzanfar et al performed annual age-specific assessments of cervical cancer in 187 countries from 1980 to 2010. The global cervical cancer incidence increased from 378,000 cases per year in 1980 to 454,000 cases per year in 2010 (annual rate of increase, 0.6%). Cervical cancer death rates have been decreasing, but the disease still accounted for 200,000 deaths in 2010; in developing countries, 46,000 of these women were aged 15-49 years, and 109,000 were aged 50 years or older.

### Age-related demographics

The Centers for Disease Control and Prevention (CDC) surveillance of screening-detected cancers (colon and rectum, breast, and cervix) in the United States from 2004 to 2006 reported that the incidence of late-stage cervical cancer was highest among women aged 50-79 years.However, cervical cancer may be diagnosed in any woman of reproductive age.

Indeed, rates of cervical adenocarcinoma have been increasing in women under 40 years of age.These cases are less easily detected with Pap test screening, and survivorship is low because cases tend to be detected at a late stage. Moreover, the HPV types causing adenocarcinoma are different from the types causing squamous carcinoma. HPV 16, which is a stronger carcinogen than other HPV types, has been found more frequently in younger women than in older ones.

### Race-related demographics

Racial variation in cervical cancer rates per 100,000 women in the United States, according to Surveillance Epidemiology and End Results (SEER) data from 2005-2009, was as follows:

* Hispanic - 11.8
* African American - 9.8
* American Indian/Alaska Native - 8.1
* White - 8.0
* Asian/Pacific Islander - 7.2

Except for Asian/Pacific Islanders, women of other races have higher mortality from cervical cancers than their White counterparts in the United States do.Death rates from cervical cancer have been highest among African Americans; however, death rates in African American women decreased by 2.6% per year from 2004 to 2008 while remaining stable in White women.

The USPSTF guidelines recommend cervical cancer screening using primary high-risk human papillomavirus (hrHPV) testing every 5 years for average-risk persons aged 30 years and older.Screening should begin at age 21 years, regardless of sexual history.

Screening recommendations for specific patient groups are as follows:

Table 1. Cervical Cancer Screening Recommendations

| Patient Status | Recommended Screening Method | Comments |
| --- | --- | --- |
| < 21 years old | No screening | Sexual history is not a consideration |
| 21-29 years old | Cytology alone every 3 years |  |
| 30-65 years old | Primary hrHPV testing alone every 5 years,  HPV and cytology cotesting every 5 years  Cytology alone every 3 years |  |
| >65 years old | Screening can be discontinued after either three consecutive negative cytology tests or two negative cytology and HPV tests within 10 years, provided the most recent test was within 5 years | Women with a history of cervical intraepithelial neoplasia (CIN) 2, CIN 3, or adenocarcinoma in situ should continue routine age-based screening for at least 20 years |
| After total hysterectomy | No screening necessary | Applies to women without a cervix and without a history of CIN 2, CIN 3, adenocarcinoma in situ, or cancer in the past 20 years |
| After HPV vaccination | Follow the same age-specific recommendations as unvaccinated women |  |

Recommend high-risk HPV testing alone every 5 years as an alternative to cytology screening alone every 3 years in women 30 years of age and older; or cotesting every 5 years.

Cervical screening should begin at age 25. Those aged 25 to 65 years should have a primary HPV test every 5 years. If primary HPV testing is not available, screening may be done with either a cotest that combines an HPV test with a Pap test every 5 years or a Pap test alone every 3 years. Those older than 65 years who have had regular screening in the past 10 years with normal results and no history of CIN2 or more serious diagnosis within the past 25 years should stop cervical cancer screening.

Guidelines for cervical cancer screening in HIV-positive women are as follows:

* HIV-positive women represent an exception to the recommendation against starting screening before age 21
* HIV-positive women younger than 30 yr can undergo cytology testing once every 3 yr instead of annually if they have had three consecutive normal annual cytology tests
* ACOG recommends against co testing for women younger than 30 yr
* Women with HIV who are 30 yr of age or older can undergo either testing with cytology alone or co testing with cytology and HPV testing; those with three consecutive normal annual cytology tests can then be screened annually, and those with one normal test result can also be screened annually

### **Management of abnormal screening results**

Guidelines for managing women with abnormal cervical cancer screening results and diagnosed cancer precursors.

* Women age 30 or older who are cytology negative but HPV positive
* Women with atypical squamous cells of undetermined significance (ASC-US) on cytology
* Women 21-24 years of age with either ASC-US or low-grade squamous intraepithelial lesion (LSIL)
* Women with LSIL
* Women 21-24 years of age with atypical squamous cells, cannot rule out high-grade SIL (ASC-H) and high-grade squamous intraepithelial lesion (HSIL)
* Women with HSIL
* Initial workup of patients with atypical glandular cells (AGC)
* Subsequent management of patients with AGC
* Women with no lesion or biopsy-confirmed grade 1 cervical intraepithelial neoplasia (CIN1) preceded by "lesser abnormalities"
* Women with no lesion or biopsy-confirmed CIN1 preceded by ASC-H or HSIL cytology
* Women 21-24 years of age with no lesion or biopsy-confirmed CIN1
* Young women with biopsy-confirmed grade 2 or 3 cervical intraepithelial neoplasia (CIN 2,3)
* Young women with biopsy-confirmed CIN 2,3 in special circumstances
* Women with unsatisfactory cytology
* Women with negative cytology but endocervical/transformation zone absent or insufficient
* Pregnant women with LSIL
* Women with atypical squamous cells; cannot exclude ASC-H
* Women diagnosed with adenocarcinoma in situ (AIS) during a diagnostic excisional procedure

**Recommendations:**

* If either (but not both) Pap smear or HPV testing yields positive results, co-testing is integrated into follow-up care; colposcopy, HPV DNA typing, or both may be indicated
* Return to "routine" screening in women treated for cervical cancer
* Colposcopy may be required for women with positive HPV results or with repeated unsatisfactory cytological findings that are missing endocervical or transformation zone components

Recommendations for cervicovaginal HPV test results as as follows:

* Women who test negative for high-risk HPV should be rescreened no sooner than every 3 years
* For women who test positive for high-risk HPV, HPV genotyping is performed, and those who test positive for HPV 16/18 are referred for colposcopy
* Those who are high-risk HPV positive but 16/18 negative undergo cervical cytology or dual stain testing
* Those with negative cytology results are rescreened in 1 year, and those with ASC-US cytology or greater are referred for colposcopy
* Extended genotyping is acceptable for patients without prior high-grade cytology (ASC-H, AGC, HSIL, or carcinoma) or histology findings of CIN grade 2, CIN grade 3, or adenocarcinoma in situ

Major recommendations with consistent scientific evidence include the recommended screening outlined in Table 1, above, and the following:

* For women with ASC-US, reflex HPV testing is preferred
* For women with HPV-positive ASC-US, whether identified on reflex HPV testing or co-testing, colposcopy is recommended
* For women with LSIL and no HPV test or a positive HPV test result, colposcopy is recommended
* For women with a histologic diagnosis of cervical intraepithelial neoplasia (CIN) 2, CIN 3, or CIN 2,3 and adequate colposcopic examination, both excision and ablation are acceptable treatment modalities, except in pregnant women and young women

Average-risk women:

* HIV infection
* Immunocompromise (eg, solid organ transplant recipients)
* Exposure to diethylstilbestrol (DES) in utero
* Previous treatment for CIN 2, CIN 3, or cancer

Annual screening for clear cell adenocarcinoma with cytology for people exposed to DES in utero until age 65 years, although screening may be continued beyond that age through shared decision-making.

### Prevention

With rare exceptions, cervical cancer recommendations for HPV vaccination:

* Routine vaccination of girls or boys aged 11-12 years with 2 or 3 doses of HPV9
* Previously unvaccinated females and males aged 13-26 years
* Children as young as 9 years may be vaccinated, particularly if there is a history of sexual abuse or assault
* Any man who has sex with a man and individuals with compromised immune systems (including people with HIV infection/AIDS), through age 26, if they were not fully vaccinated when they were younger

## 

## **Chemotherapy Agents, Alkylating**

Alkylating chemotherapy agents inhibit cell growth and proliferation. They inhibit DNA synthesis through the formation of DNA cross-links.

## Cisplatin (Platinol)

Intrastrand cross-linking of DNA and inhibition of DNA precursors are among the proposed mechanisms of action for cisplatin. This agent is used in combination with radiation therapy.

## Ifosfamide (Ifex)

Ifosfamide forms DNA interstrand and intrastrand bonds that interfere with protein synthesis. Although the US Food and Drug Administration (FDA) has approved this agent only for the treatment of testicular cancer, it has several off-label indications, including treatment of cervical cancer.

## **Antineoplastics, Antimetabolite**

## 

Antimetabolite antineoplastic agents inhibit cell growth and proliferation. They interfere with DNA synthesis by blocking the methylation of deoxyuridylic acid.

## Fluorouracil (Adrucil)

Fluorouracil is a pyrimidine antimetabolite. Several mechanisms of action have been proposed, including inhibition of thymidylate synthase and inhibition of RNA synthesis. This agent is also a potent radiosensitizer.

## **Antineoplastics, Anti microtubular**

## 

Anti microtubular antineoplastic agents prevent cell growth and proliferation. They work by enhancing tubulin dimers, stabilizing existing microtubules, and inhibiting their disassembly.

## Paclitaxel (Taxol)

The mechanisms of action of paclitaxel are tubulin polymerization and microtubule stabilization. This agent also participates in the breakage of chromosomes and modulation of immune response.

## **Antineoplastics, Topoisomerase Inhibitors**

## 

Topoisomerase-inhibiting antineoplastic agents prevent cell growth and proliferation. They work by binding to topoisomerase and causing single-strand DNA breaks.

## Topotecan (Hycamtin)

Topotecan inhibits topoisomerase I, inhibiting DNA replication. It acts in the S phase of the cell cycle. Patients who have received prior chemotherapy should be given a lower dose initially.

## **Antineoplastics, VEGF Inhibitor**

## 

Vascular endothelial growth factor (VEGF) is crucial to angiogenesis. VEGF inhibitors directly bind to the VEGF protein to disrupt angiogenesis.

## Bevacizumab (Avastin)

Bevacizumab is a recombinant humanized monoclonal antibody to VEGF. It blocks the angiogenic molecule VEGF, thereby inhibiting tumor angiogenesis and starving the tumor of blood and nutrients. It is indicated as part of a combination chemotherapy regimen for persistent, recurrent, or metastatic carcinoma of the cervix.

## **PD-1/PD-L1 Inhibitors**

## 

Monoclonal antibodies that bind the programmed cell death-1 protein (PD-1) ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production.

## Pembrolizumab (Keytruda)

Indicated for treatment of recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS 1 or greater) as determined by an FDA-approved test. Pembrolizumab is also indicated for unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mut/Mb] solid tumors in patients that have progressed following prior treatment and who have no alternative treatment options.

## **Vaccines, Inactivated, Viral**

## 

The 9-valent HPV vaccine is indicated for prevention of HPV-associated neoplasias and precancerous genital lesions. The 2-valent and 4-valent vaccines were discontinued from the US market in 2016.

Children and adolescents aged 15 years and younger need two, not three, doses of the HPV vaccine; this ACIP recommendation stems from the vaccine’s enhanced immunogenicity in preteens and adolescents aged 9-14 years. The schedule for older adolescents and young adults aged 15 through 45 years is three inoculations within 6 months.

## Human papillomavirus vaccine, nonavalent (Gardasil 9)

Recombinant vaccine that targets 9 HPV types (6, 11, 16, 18, 31, 33, 45, 52, and 58). It is indicated for females aged 9 through 45 years to prevent cervical, vulvar, vaginal, and anal cancer. It is also indicated to prevent genital warts and dysplastic lesions (eg, cervical, vulvar, vaginal, anal). It is also indicated for males aged 9 through 45 years for prevention of neoplasias and dysplasias (eg, anal cancer).

## Human papillomavirus vaccine, bivalent (Cervarix)

October 21, 2016: HPV bivalent vaccine discontinued in the United States.

The bivalent recombinant HPV vaccine is prepared from the L1 protein of HPV types 16 and 18. It is indicated for girls and women (ages 9-25 years) to prevent the following diseases caused by oncogenic HPV types 16 and 18:

- Cervical cancer

- CIN grade 2 or higher

- Cervical adenocarcinoma in situ

- CIN grade 1

## **Outlook / Prognosis**

Cervical cancer is serious, but it’s highly treatable, especially in the early stages. If you do receive a diagnosis, it’s normal to worry about your health or feel angry that cancer has happened to you. You want the cancer to go away so you can continue living a long and fulfilling life. Ask your healthcare provider about what treatment they recommend.

Cancer treatment can be difficult and cause unpleasant side effects. Lean on your loved ones for help. Support groups for people with cancer can also be helpful when you need someone to understand what you’re going through.

Once treatment is over, your healthcare provider will want to monitor you closely to ensure the cancer doesn’t come back. Even if you reach remission, you’ll likely always have cancer in the back of your brain, feeling worried that it can come back. This is a normal response to having cancer. Talking through your feelings with a counselor, close friend or healthcare provider can be beneficial.

#### **What are the survival rates for cervical cancer?**

Survival rates for cervical cancer are very good, especially when your provider catches cells at the precancer level (before they change to cancer cells). According to the National Cancer Institute, the five-year relative survival rates are:

* If cervical cancer hasn’t spread, the five-year relative survival rate is 91%. Almost half of all cervical cancers are diagnosed at this stage.
* If cervical cancer has spread outside your cervix to nearby tissues, the five-year relative survival rate is 60%.
* If cervical cancer has spread to your lymph nodes and distant organs, the five-year relative survival rate is about 19%.

These statistics don’t necessarily predict what will happen to you. Your healthcare provider is the best person to discuss your outlook which is unique to you.

### **When should I see my healthcare provider?**

You should contact a healthcare provider if you develop abnormal or suspicious symptoms. Some things to watch for include:

* Bleeding between menstrual periods or after menopause.
* Watery vaginal discharge.
* Pelvic pain or pain during sex.

Contact your healthcare provider if you’re unsure when your last Pap test was. They can get you on a regular schedule to ensure any changes to your cervix are caught early.

## **Cervical Cancer: Common Patient Questions and Answers**

What is cervical cancer?  
Cervical cancer is a malignant growth that starts in the cervix, the lower part of the uterus connecting to the vagina. It is most often caused by persistent infection with high-risk types of human papillomavirus (HPV).

What causes cervical cancer?  
The primary cause is HPV infection, particularly high-risk strains. Other risk factors include smoking, having multiple sexual partners, a weakened immune system, and long-term use of oral contraceptives.

What are the symptoms?  
Early cervical cancer may have no symptoms. When present, symptoms can include abnormal vaginal bleeding (between periods, after intercourse, or after menopause), unusual vaginal discharge, pelvic pain, pain during sex, and, in advanced cases, leg swelling, weight loss, or fatigue.

How common is cervical cancer?  
Globally, cervical cancer is the fourth most common cancer in women, with about 660,000 new cases and 350,000 deaths in 2022.

How can I lower my risk or prevent cervical cancer?

* Get the HPV vaccine.
* Attend regular cervical screening (Pap smear and/or HPV testing) as recommended for your age group.
* Practice safe sex and limit the number of sexual partners.
* Don’t smoke.
* Maintain a healthy lifestyle.

What are the cervical cancer screening recommendations?

* Start screening at age 21.
* Ages 21–29: Pap test every 3 years.
* Ages 30–65: Pap test every 3 years, or HPV test every 5 years, or co-testing every 5 years.
* Screening can usually stop after age 65 if you’ve had normal results for many years.

If I have risk factors, should I consider preventive surgery?  
Unlike breast or ovarian cancer, there is no recommended preventive surgery for cervical cancer. The best prevention is regular screening and HPV vaccination.

What are my treatment options if I am diagnosed?  
Treatment depends on the stage and may include:

* Surgery (for early-stage disease)
* Radiation therapy
* Chemotherapy
* Targeted therapy or immunotherapy (for advanced cases)  
  Your care team will recommend a plan based on your cancer’s stage, type, and your overall health.

What are the side effects of treatment?  
Side effects depend on the treatment and may include fatigue, nausea, changes in menstruation, early menopause, infertility, and sexual or urinary changes. Your care team will help manage side effects.

Can cervical cancer be cured?  
Yes, cervical cancer can often be cured if detected and treated early. Advanced cases are more challenging but treatments can control the disease and improve quality of life.

Will I be able to have children after treatment?  
Some treatments may affect fertility. If you wish to have children in the future, discuss fertility-preservation options with your doctor before starting treatment.

What if my cancer comes back?  
Your care team will discuss additional treatment options and supportive care if the cancer recurs.

Is there anything else I should do?

* Attend all follow-up appointments.
* Maintain a healthy lifestyle.
* Seek support from family, friends, or support groups.
* Ask your healthcare team any questions you have and request additional resources as needed.

**Most Common Mutations:**

* + PIK3CA: The most frequently mutated gene in cervical cancer, present in about 15–36% of cases, and particularly common in squamous cell carcinoma (SCC) compared to adenocarcinoma (ADC). The E545K and E542K are notable hotspot mutations, and PIK3CA mutations are associated with poorer survival and resistance to some chemotherapies.
  + KRAS: Mutations found mainly in adenocarcinoma (up to 17.5%) and rarely in SCC. KRAS mutations are associated with HPV-18 infection and worse prognosis.
  + EGFR: Rare, but present in both SCC and ADC, with some mutations unique to SCC.
  + ARID1A, FBXW7, NOTCH1, FGFR3, EP300, TP53: Other recurrently mutated genes, each found in 10–25% of cases.
  + ERBB3, MED1, CASP8, HLA-A, TGFBR2: Additional mutated genes identified in large sequencing studies.
  + PTEN, MAPK1, STK11: Less common but relevant for tumor progression and therapy.
* Immune-Related and Targetable Alterations:
  + CD274 (PD-L1) and PDCD1LG2: Alterations in these immune checkpoint genes may make tumors susceptible to immunotherapy.
  + Tumors with BCAR4 fusions: May be sensitive to lapatinib, a drug used in breast cancer.
* Pathway Involvement:
  + Nearly 75% of cervical cancers have alterations in the PI3K/MAPK and TGF-beta signaling pathways, providing multiple potential therapeutic targets.
  + APOBEC3-induced mutations are common, reflecting the role of viral (HPV) infection in mutagenesis.

## Genomic Differences by Subtype and HPV Type

* Squamous Cell Carcinoma (SCC):
  + Higher rates of PIK3CA mutations.
  + Unique mutations in EP300 and MAPK1 have been reported.
* Adenocarcinoma (ADC):
  + KRAS mutations are more common.
  + FBXW7 and STK11 mutations are also notable.
* HPV Type Influence:
  + HPV16-positive tumors have more PIK3CA mutations.
  + HPV18/45-positive tumors are more likely to have multiple hotspot mutations, especially in ADC.

## Hereditary Syndromes and Rare Genetic Risks

* DICER1 syndrome and Peutz-Jeghers syndrome (PJS): Rare hereditary conditions that increase risk for uncommon cervical cancers, such as embryonal rhabdomyosarcoma.

## Clinical Implications

* Targeted Therapy:
  + PIK3CA, KRAS, and immune checkpoint mutations may be actionable with targeted agents or immunotherapy.
  + Genomic profiling can guide personalized therapy, especially in advanced or recurrent disease.
* Prognosis:
  + PIK3CA and KRAS mutations are associated with worse outcomes and may predict resistance to standard treatments

## **Doctor-Patient Conversation: Cervical Cancer**

Doctor: Thank you for coming in today. I have your test results, and I’d like to discuss them with you. The diagnosis is cervical cancer.

Patient: That’s a lot to take in. What does this mean for me?

Doctor: I understand this is difficult news. Cervical cancer means there are malignant cells in the cervix. The next step is to determine the stage of the cancer—how far it has progressed. This helps us decide on the best treatment options for you and gives us an idea of your outlook.

Patient: What kind of treatment will I need?

Doctor: Treatment depends on the stage and your overall health. Early-stage cancer is often treated with surgery, while more advanced cases may require radiation, chemotherapy, or a combination. We’ll discuss the best plan for you once we have all the staging information.

Patient: Is this something that can be cured?

Doctor: Many cases of cervical cancer can be cured, especially if detected early. Even in more advanced cases, treatment can control the disease and help you feel better for as long as possible.

Patient: What should I do next?

Doctor: We’ll arrange for further tests to determine the stage. I encourage you to write down any questions or concerns you have and bring them to your next appointment. It’s also helpful to bring a family member or friend for support and to help remember the information we discuss.

Patient: I’m worried about the treatment and side effects.

Doctor: That’s understandable. We’ll talk through each treatment option, what to expect, and how we can help manage any side effects. You have the right to ask questions at any time, and we’ll work together to make decisions that are right for you.

Patient: How can I make sure I understand everything?

Doctor: If anything is unclear, please ask me to explain it again or in a different way. You can repeat back what you’ve heard to make sure it matches your understanding. If you prefer, I can provide written information or visual aids. You can also record our conversation or take notes if that helps.

Patient: Is there anything else I should know?

Doctor: It’s important to attend all follow-up appointments and screenings. We’ll also connect you with support services if you need help coping emotionally or practically. Remember, you’re not alone—we’re here to support you every step of the way

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**ENDOMETRIAL CANCER**

**DEFINITION AND DESCRIPTION**

Endometrial cancer is a type of cancer that begins as a growth of cells in the uterus. The uterus is the hollow, pear-shaped pelvic organ where fetal development happens.

Endometrial cancer begins in the layer of cells that form the lining of the uterus, called the endometrium. Endometrial cancer is sometimes called uterine cancer. Other types of cancer can form in the uterus, including uterine sarcoma, but they are much less common than endometrial cancer.

Endometrial cancer is often found at an early stage because it causes symptoms. Often the first symptom is irregular vaginal bleeding. If endometrial cancer is found early, surgically removing the uterus often cures it.

**Causes**

The cause of endometrial cancer isn't known. What's known is that something happens to cells in the lining of the uterus that changes them into cancer cells.

Endometrial cancer starts when cells in the lining of the uterus, called the endometrium, get changes in their DNA. A cell's DNA holds the instructions that tell the cell what to do. The changes tell the cells to multiply quickly. The changes also tell the cells to continue living when healthy cells would die as part of their natural life cycle. This causes a lot of extra cells. The cells might form a mass called a tumor. The cells can invade and destroy healthy body tissue. In time, the cells can break away and spread to other parts of the body.

**RISK FACTORS**

Factors that increase the risk of endometrial cancer include:

* **Changes in the balance of hormones in the body.** The two main hormones the ovaries make are estrogen and progesterone. Changes in the balance of these hormones cause changes in the endometrium.  
  A disease or condition that increases the amount of estrogen, but not the level of progesterone, in the body can increase the risk of endometrial cancer. Examples include obesity, diabetes and irregular ovulation patterns, which might happen in polycystic ovary syndrome. Taking hormone therapy medicine that contains estrogen but not progestin after menopause increases the risk of endometrial cancer.  
  A rare type of ovarian tumor that gives off estrogen also can increase the risk of endometrial cancer.
* **More years of menstruation.** Starting menstruation before age 12 or beginning menopause later increases the risk of endometrial cancer. The more periods you've had, the more exposure your endometrium has had to estrogen.
* **Never having been pregnant.** If you've never been pregnant, you have a higher risk of endometrial cancer than someone who has had at least one pregnancy.
* **Older age.** As you get older, your risk of endometrial cancer increases. Endometrial cancer occurs most often after menopause.
* **Obesity.** Being obese increases your risk of endometrial cancer. This may happen because extra body fat can alter your body's balance of hormones.
* **Hormone therapy for breast cancer.** Taking the hormone therapy medicine tamoxifen for breast cancer can increase the risk of developing endometrial cancer. If you're taking tamoxifen, talk about the risk with your health care team. For most, the benefits of tamoxifen outweigh the small risk of endometrial cancer.
* **An inherited syndrome that increases the risk of cancer.** Lynch syndrome increases the risk of colon cancer and other cancers, including endometrial cancer. Lynch syndrome is caused by a DNA change that's passed from parents to children. If a family member has been diagnosed with Lynch syndrome, ask your health care team about your risk of this genetic syndrome. If you've been diagnosed with Lynch syndrome, ask what cancer screenings you need.

**Symptoms**

Symptoms of endometrial cancer may include:

* Vaginal bleeding after menopause.
* Bleeding between periods.
* Pelvic pain.

### **When to see a doctor**

Make an appointment with a healthcare professional if you experience any symptoms that worry you.

**DIAGNOSIS**

Tests and procedures used to diagnose endometrial cancer include:

* **Examining the pelvis.** A pelvic exam checks the reproductive organs. It's often done during a regular checkup, but it might be needed if you have symptoms of endometrial cancer.  
  During the exam, a health care professional carefully inspects the outer genitals. Two fingers of one hand are inserted into the vagina and the other hand presses on the abdomen to feel the uterus and ovaries. A device called a speculum is inserted into the vagina. The device opens the vaginal canal so the health professional can look for signs of cancer or other problems.
* **Imaging tests.** Imaging tests make pictures of the inside of the body. They can tell your health care team about your cancer's location and size. One imaging test might be a transvaginal ultrasound. In this procedure, a wandlike device called a transducer is inserted into the vagina. The transducer uses sound waves to create a video image of the uterus. The image shows the thickness and texture of the endometrium. Ultrasound can help your health care team look for signs of cancer and rule out other causes for your symptoms. Other imaging tests such as MRI and CT scans also may be suggested.
* **Using a scope to examine your endometrium, called a hysteroscopy.** During a hysteroscopy, a health care professional inserts a thin, flexible, lighted tube through the vagina and cervix into the uterus. This tube is called a hysteroscope. A lens on the hysteroscope allows the health professional to examine the inside of the uterus and the endometrium.
* **Removing a sample of tissue for testing, called a biopsy.** In an endometrial biopsy, a sample of tissue is removed from the lining of the uterus. Endometrial biopsy often is done in a health care professional's office. The sample is sent to a lab for testing to see if it is cancer. Other special tests give more details about the cancer cells. Your health care team uses this information to make a treatment plan.
* **Performing surgery to remove tissue for testing.** If enough tissue can't be obtained during a biopsy or if the biopsy results are unclear, you'll likely need to undergo a procedure called dilation and curettage, also called D&C. During D&C, tissue is scraped from the lining of the uterus and examined under a microscope for cancer cells.

If endometrial cancer is found, you'll likely be referred to a doctor who specializes in treating cancers involving the reproductive system, called a gynecologic oncologist.

### **Staging endometrial cancer**

Once your cancer has been diagnosed, your health care team works to determine the extent of your cancer, called the stage. Tests used to determine your cancer's stage may include a chest X-ray, a CT scan, blood tests and positron emission tomography, also called a PET scan. Your cancer's stage may not be known until after you have surgery to treat your cancer.

Your health care team uses information from these tests and procedures to assign your cancer a stage. The stages of endometrial cancer are indicated using numbers ranging from 1 to 4. The lowest stage means that the cancer hasn't grown beyond the uterus. By stage 4, the cancer has grown to involve nearby organs, such as the bladder, or has spread to distant areas of the body.

* Stage IA\* - No or less than half myometrial invasion
* Stage IB\* - Invasion equal to or more than half of the myometrium
* Stage II\* - Tumor invades cervical stroma but does not extend beyond the uterus\*\*
* Stage III - Local and/or regional spread of the tumor
* Stage IIIA\* - Tumor invades the serosa of the corpus uteri and/or adnexa†
* Stage IIIB\* - Vaginal metastasis and/or parametrial involvement†
* Stage IIIC\* - Metastases to pelvic and/or para-aortic lymph nodes
* Stage IIIC1\* - Positive pelvic nodes
* Stage IIIC2\* - Positive para-aortic lymph nodes with or without positive pelvic nodes
* Stage IV\* - Tumor invasion of bladder and/or bowel mucosa and/or distant metastases
* Stage IVA\* - Tumor invasion of bladder and/or bowel mucosa
* Stage IVB\* - Distant metastases, including intra-abdominal and/or inguinal lymph node

Cases of carcinoma of the corpus should be classified (or graded) according to the degree of histologic differentiation. The histopathology and degree of differentiation is as follows:

* Class G1 - Non squamous or non morular solid growth pattern of 5% or less
* Class G2 - Non squamous or non morular solid growth pattern of 6-50%
* Class G3 - Non squamous or non morular solid growth pattern of more than 50%

\* Either G1, G2, or G3.

\*\* Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.

† Positive cytology has to be reported separately without changing the stage.

**Treatment**

Endometrial cancer is usually first treated with surgery to remove the cancer. This may include removing the uterus, fallopian tubes and ovaries. Other treatment options may include radiation therapy or treatments using medicines to kill the cancer cells. Options for treating your endometrial cancer will depend on the characteristics of your cancer, such as the stage, your general health and your preferences.

### **Surgery**

Treatment for endometrial cancer usually involves an operation to remove the uterus, called a hysterectomy. Treatment also usually includes the removal of the fallopian tubes and ovaries, called a salpingo-oophorectomy. A hysterectomy makes it impossible for you to become pregnant in the future. Also, once your ovaries are removed, you'll experience menopause if you haven't already.

During surgery, your surgeon also will inspect the areas around your uterus to look for signs that cancer has spread. Your surgeon also may remove lymph nodes for testing. This helps determine your cancer's stage.

### **Radiation therapy**

Radiation therapy uses powerful energy to kill cancer cells. The energy can come from X-rays, protons or other sources. In certain situations, radiation therapy may be recommended before surgery. Radiation therapy can shrink a tumor and make it easier to remove.

If you aren't healthy enough to undergo surgery, you may opt for radiation therapy only.

Radiation therapy can involve:

* **Radiation from a machine outside your body.** During external beam radiation, you lie on a table while a machine directs radiation to specific points on your body.
* **Radiation placed inside your body.** Internal radiation, called brachytherapy, involves a radiation-filled device, such as small seeds, wires or a cylinder. This device is placed inside your vagina for a short period of time.

### **Chemotherapy**

Chemotherapy uses strong medicines to kill cancer cells. Some people receive chemotherapy medicine. Others receive two or more medicines together. Most chemotherapy medicines are given through a vein, but some are taken in pill form. These medicines enter the bloodstream and then travel through the body, killing cancer cells.

Chemotherapy is sometimes used after surgery to lower the risk that the cancer might return. Chemotherapy also can be used before surgery to shrink the cancer. This makes it more likely that the cancer is removed completely during surgery.

Chemotherapy may be recommended for treating advanced endometrial cancer that has spread beyond the uterus or to treat cancer that has come back.

### **Hormone therapy**

Hormone therapy involves taking medicines to lower the hormone levels in the body. In response, cancer cells that rely on hormones to help them grow might die. Hormone therapy may be an option if you have advanced endometrial cancer that has spread beyond the uterus.

### **Targeted therapy**

Targeted therapy uses medicines that attack specific chemicals in cancer cells. By blocking these chemicals, targeted treatments can cause cancer cells to die. Targeted therapy is usually combined with chemotherapy for treating advanced endometrial cancer.

### **Immunotherapy**

Immunotherapy uses medicine that helps the body's immune system kill cancer cells. The immune system fights off diseases by attacking germs and other cells that shouldn't be in the body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells. For endometrial cancer, immunotherapy might be considered if the cancer is advanced and other treatments haven't helped.

### **Palliative care**

Palliative care is a special type of health care that helps you feel better when you have a serious illness. If you have cancer, palliative care can help relieve pain and other symptoms. Palliative care is done by a team of healthcare professionals. This can include doctors, nurses and other specially trained professionals. Their goal is to improve the quality of life for you and your family.

Palliative care specialists work with you, your family and your care team to help you feel better. They provide an extra layer of support while you have cancer treatment. You can have palliative care at the same time as strong cancer treatments, such as surgery, chemotherapy or radiation therapy.

When palliative care is used along with all of the other appropriate treatments, people with cancer may feel better and live longer.

**Prevention**

To reduce your risk of endometrial cancer, you may wish to:

* **Talk to your health care team about the risks of hormone therapy after menopause.** If you're considering hormone replacement therapy to help control menopause symptoms, ask about the risks and benefits. Unless you've had your uterus removed, replacing estrogen alone after menopause may increase your risk of endometrial cancer. A hormone therapy medicine that combines estrogen and progestin can reduce this risk. Hormone therapy carries other risks, so weigh the benefits and risks with your health care team.
* **Consider taking birth control pills.** Using oral contraceptives for at least one year may reduce endometrial cancer risk. Oral contraceptives are contraceptives that are taken in pill form. They also are called birth control pills. The risk reduction is thought to last for several years after you stop taking oral contraceptives. Oral contraceptives have side effects, though, so discuss the benefits and risks with your health care team.
* **Maintain a healthy weight.** Obesity increases the risk of endometrial cancer, so work to achieve and maintain a healthy weight. If you need to lose weight, increase your physical activity and reduce the number of calories you eat each day.

**QUESTION AND ANSWER SET**

## What's the most likely cause of my symptoms?

The most likely cause of symptoms such as abnormal vaginal bleeding (especially after menopause), pelvic pain, or unusual discharge is a problem with the lining of the uterus. While endometrial cancer is a concern, other conditions like polyps, fibroids, or hormonal changes can also cause these symptoms.

## Are there any other possible causes for my symptoms?

Yes. Other possible causes include benign endometrial polyps, uterine fibroids, endometrial hyperplasia, hormonal imbalances, and, less commonly, infections or other cancers (such as cervical cancer).

## What tests do I need to diagnose endometrial cancer?

Diagnosis usually involves:

* Pelvic exam
* Transvaginal ultrasound to assess the uterus lining
* Endometrial biopsy (removal of a small tissue sample from the uterus lining)
* Sometimes, hysteroscopy (a camera to look inside the uterus) or dilation and curettage (D&C) if the biopsy is inconclusive.

## Are there other tests for staging the cancer?

Yes. Staging may require:

* Imaging tests such as CT, MRI, or PET scans to check for spread
* Surgical staging during hysterectomy, which may include removal and testing of lymph nodes and inspection of nearby tissues.

## What treatments are available? What side effects can I expect from each treatment? How will these treatments affect my sexuality?

* Surgery (hysterectomy): Main treatment; removes uterus (and often ovaries/fallopian tubes). Side effects: surgical risks, immediate menopause if ovaries are removed, potential impact on sexual function (vaginal shortening, dryness, loss of fertility).
* Radiation therapy: May cause fatigue, digestive problems, vaginal dryness, burning, or tightening, and can affect sexual intimacy.
* Chemotherapy: Side effects include fatigue, nausea, vomiting, hair loss, neuropathy, anemia, and increased infection risk. Some drugs may cause heart or kidney damage, or bladder irritation.
* Hormonal therapy: Can cause bloating, weight gain, fluid retention, hot flashes, and vaginal dryness.
* Immunotherapy/Targeted therapy: Side effects vary but may include fatigue, rash, diarrhea, high blood pressure, or thyroid problems. Some combinations can be more effective but also have unique side effects.

## What do you think is the best course of action for me?

The best approach depends on the cancer’s stage, type, and your overall health. Surgery is usually the first step, often followed by radiation, chemotherapy, or hormone therapy if needed. Your care team will tailor the plan to your specific situation.

## What are the alternatives to the primary approach that you're suggesting?

Alternatives may include hormone therapy (for those who cannot have surgery), radiation alone, or participation in clinical trials for new treatments. The choice depends on your health, cancer stage, and personal preferences.

## I have other health conditions. How can I best manage them together?

Your care team will coordinate with your other doctors to manage existing conditions (like diabetes, heart disease, or high blood pressure) and adjust cancer treatment as needed to minimize risks and interactions.

## Are there any restrictions that I need to follow?

You may need to avoid strenuous activity after surgery, follow special instructions during radiation or chemotherapy, and avoid certain foods or medications as advised. Sexual activity may be restricted during and after some treatments, especially radiation.

## Has my cancer spread? What stage is it?

Staging is determined by imaging and surgical findings. Stages range from I (confined to the uterus) to IV (spread to distant organs). Sometimes, the exact stage is only known after surgery.

## What's my prognosis?

Prognosis depends on the stage, grade, and type of endometrial cancer, as well as your overall health. Early-stage cancers have an excellent prognosis; advanced stages are more challenging but still treatable.

## Should I see a specialist? What will that cost, and will my insurance cover it?

You should see a gynecologic oncologist for specialized care. Costs and insurance coverage vary; your care team or insurance provider can help clarify coverage and out-of-pocket costs

### **What are the warning signs of uterine cancer?**

Let your provider know about any irregular bleeding. Abnormal bleeding includes bleeding between periods if you still menstruate and bleeding or spotting if you’re postmenopausal. Abnormal bleeding is a symptom of many conditions, including endometrial cancer.

### **Does uterine cancer spread quickly?**

Type 1 cancers, the most common type, don’t spread quickly. Type 2 cancers can spread quickly and may require more aggressive treatment.

### **At what age is endometrial cancer most common?**

Endometrial cancer is most common in people who’ve gone through menopause. The average age of menopause is 51.

## **Outlook / Prognosis**

### **What’s the survival rate for people with uterine cancer?**

The five-year survival rate for endometrial cancer is 81%. That means 81% of women diagnosed with the disease are alive five years later. The rate is even higher when cancer hasn’t spread outside your uterus. Then, the survival rate reaches as high as 95%. Treatments continue to improve, along with survival rates. Uterine cancer is fatal when it goes undiagnosed and spreads. The survival rate decreases to 17% when cancer spreads to other parts of your body outside your uterus. Early detection and early treatment are key to a favorable prognosis.

### **Is there a cure for uterine cancer?**

Fortunately, endometrial cancer is often diagnosed at an early stage. That’s because many people notice unusual bleeding and tell their healthcare providers. If cancer gets caught early and hasn’t spread to other organs, removing your uterus can cure it.

## **Diagnostic Considerations**

Bleeding from the lower genital tract can occur from the cervix, vulva, or vagina. If the bleeding is due to neoplasms, gross inspection usually helps identify these lesions. If cervical cytology findings are abnormal and no gross lesions are identified, further evaluation must be performed.

Atrophic changes in the vagina may lead to bleeding, particularly postcoital. Bleeding from the uterus may be due to any of the many types of benign lesions (eg, polyps, endometritis) or to hormone replacement therapy.

## Important considerations

Ignored irregular postmenopausal bleeding could lead to a delay in diagnosis and treatment, which may impact survival.

## Special concerns

Multiple new prognostic factors of endometrial cancer are being evaluated and are brought about by newer technology, which allows for molecular biological evaluation. Because these evaluations are new, no general agreement has been reached about their importance. Note the following:

* Flow cytometry has been used in ploidy analysis (cellular nuclear DNA content) and to measure the proliferative fraction of tumor cells (S phase).
* The prognostic factors of the endometrial cancer precursor 1 score (ie, myometrial invasion, DNA ploidy, and mean shortest nuclear axis) have been evaluated, and in at least one study, multivariate analysis was noted to be important prognostically.
* Several other molecular biological characteristics have been noted to be important prognostically, including *HER2/NEU* and *TP53* gene overexpression.
* Newer characteristics are being identified almost daily. Obviously, the necessity for standardization is needed before applicability is available and conclusions can be reached. As experience is gained with these factors, they may be the new prognostic factors for endometrial cancer.

The use of pelvic and para-aortic lymphadenectomy in the management of adenocarcinoma of the endometrium is controversial, as follows:

* Whether the procedure aids in diagnosis is not in doubt. The question that has been raised is whether or not it also might be therapeutic. It certainly appears to be therapeutic for other gynecological cancers. Retrospective data by Kilgore and colleagues suggest that lymphadenectomy in endometrial cancer can also be therapeutic.
* The number of lymph nodes removed appears therapeutic even if positive nodes are present. In evaluating the SEER data, Chan has noted that patients with positive lymph nodes but few total nodes removed had a worse prognosis than if multiple nodes were removed.
* When proposed, the FIGO surgical staging classification was questioned as being efficacious by many investigators. However, data suggest that the gynecologic oncology community worldwide has accepted the surgical staging classification. In fact, lymphadenectomies are being performed routinely by these investigators.

**EPIDEMIOLOGY**

Endometrial cancer is the most common cancer of the female genital tract and the fourth most common cancer overall in women in the United States, with approximately 61,880 newly diagnosed cases and 12,160 deaths reported annually.Globally, endometrial cancer has a peak incidence in those between 65 and 75 years. Though the incidence remains highest in North America, the worldwide incidence of this malignancy has increased by more than 130% within the past 30 years.

The average age for type 1 endometrial cancer diagnosis in the United States decreased from 64 to 61 years, which some experts have posited is secondary to increasing obesity rates. Some study results have estimated the incidence of endometrial cancer will double to 122,000 cases annually by the year 2030. The incidence of endometrial cancer is also increasing more significantly in Hispanic, Asian, Pacific Islander, and Black women than in non-Hispanic White women. Moreover, Black women have a higher incidence of advanced, high-grade cancers at the time of diagnosis, as well as poorer outcomes than non-Hispanic White women, which may be due to socioeconomic and health care access disparitie

**RECOMMENDATIONS**

the time of menopause, all women should be made aware of the risks and symptoms of endometrial cancer and strongly encouraged to report any unexpected bleeding or spotting to their physician

patients who are taking tamoxifen. Metrorrhagia should always be investigated in postmenopausal women or those with risk factors, using transvaginal ultrasound with a cutoff level of 3 mmLynch syndrome

Women with Lynch syndrome (hereditary nonpolyposis colorectal cancer) have up to an 80% increased risk for colorectal cancer and a 60% increased risk for endometrial cancer.

all individuals diagnosed with colorectal or endometrial cancers to identify which patients should have genetic testing for Lynch syndrome. In addition, Lynch syndrome genetic testing should be done for all women diagnosed with endometrial cancer before age 50 and family members of anyone with Lynch syndrome

* Hysterectomy and bilateral salpingo-oophorectomy should be offered to women who have completed child bearing and carry *MLH1*, *MSH2*, or *MSH6* mutations
* Annual endometrial sampling for carriers of *MLH1* or *MSH2*
* Annual colonoscopy (to decrease risk of colorectal cancer)
* Routine transvaginal ultrasound and serum CA-125 testing are not recommended

Genetic testing is preferred when resources are available, but clinical screening that includes focused family history is acceptable. Asymptomatic women with a first-degree relative diagnosed with either endometrial or colorectal cancer before age 60 should also be testedColonoscopy every 1-2 years, beginning at age 20-25

* Endometrial sampling every 1-2 years beginning at age 30-35
* Prophylactic hysterectomy and bilateral salpingo-oophorectomy should be offered to women in their early to mid-40s

biopsy starting from the age of 35 until hysterectomy for all Lynch syndrome mutation carriers. In addition, for management of women with Lynch syndrome, recommendations include:

* Annual screening beginning at age 35
* Regular hysteroscopy and endometrial biopsies
* The application of local progesterone using the levonorgestrel intrauterine device
* Treatment of premalignant disease (ie, atypical endometrial hyperplasia or endometrial intraepithelial neoplasia)
* Hysterectomy and bilateral oophorectomy
* After total hysterectomy, no radiation therapy is required for patients with grade 1 or 2 tumors with < 50% myometrial invasion
* Vaginal brachytherapy is an option for patients with grade 3 tumors without myometrial invasion or grade 1 or 2 tumors with high risk factors
* Vaginal brachytherapy is comparable to pelvic radiation in preventing recurrence for patients with grade 1 or 2 tumors ≥50% myometrial invasion; or grade 3 tumors with < 50% myometrial invasion; vaginal brachytherapy is preferred
* Pelvic radiation for patients with grade 3 tumors with ≥50% myometrial invasion or cervical stroma invasion; or grade 1 or 2 tumors with ≥50% myometrial invasion with high risk factors
* For patients with positive nodes, or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum: external beam radiation therapy as well as adjuvant chemotherapy
* Use of vaginal brachytherapy in patients also undergoing pelvic external beam radiation is not generally warranted
* For patients with metastatic disease, concurrent chemoradiation followed by adjuvant chemotherapy is indicated; alternative sequencing strategies with external beam radiation and chemotherapy are also acceptable

**Adjuvant treatment recommendations are as follows:**

* Low-risk patients – Adjuvant treatment not required
* Intermediate-risk patients – Vaginal brachytherapy (VBT); VBT plus pelvic radiation in patients with no surgical nodal staging
* High-risk patients - Adjuvant chemotherapy (carboplatin-paclitaxel) with concurrent or sequential external beam radiation therapy, or chemotherapy alone

Hormonal therapy could be an appropriate therapeutic alternative for patients with low-grade, hormone-receptor–positive disease, without rapidly progressive metastatic disease. The treatment of choice is progestogens or progestogens alternating with tamoxifen.

Pembrolizumab plus lenvatinib should be considered for second-line treatment, particularly for mismatch repair (MMR)–proficient tumors; dostarlimab or pembrolizumab can be considered for second-line therapy of MMR-deficient tumors.

* Combination chemotherapy and radiation therapy should be considered before a single-modality treatment
* Chemotherapy with a paclitaxel with carboplatin regimen is as effective as other regimens and had less toxicity
* For treatment of metastatic disease, hormonal therapy with progestational agents may be considered; tamoxifen and aromatase inhibitors are also acceptable [31]
* Based on preliminary studies, a targeted agent such as temsirolimus or ridaforolimus may be considered as a second-line agent [31]
* For patients with microsatellite instability–high/mismatch repair–deficient disease, immune checkpoint blockade therapy can be considered following platinum-based treatment failure

**GENOMIC DATA**

| **Subtype** | **Key Features & Mutations** | **Prognosis** |
| --- | --- | --- |
| POLE ultramutated (POLEmut) | Mutations in the exonuclease domain of the POLE gene; extremely high mutation burden | Excellent prognosis |
| MMRd/MSI-H (Mismatch Repair Deficient/Hypermutated) | Defective mismatch repair genes (e.g., MLH1, MSH2, MSH6, PMS2); high microsatellite instability | Intermediate prognosis, good response to immunotherapy |
| NSMP (No Specific Molecular Profile, “copy number low”) | Lacks POLE, MMRd, and p53 mutations; often has CTNNB1, PTEN, PIK3CA, ARID1A mutations | Intermediate prognosis |
| p53 abnormal (“copy number high”) | TP53 mutations; extensive copy number alterations; often serous or high-grade tumors |  |

## 

## **Doctor-Patient Conversation: Endometrial Cancer**

Doctor: Thank you for coming in today. I have your test results, and I’d like to talk with you about them. The diagnosis is endometrial cancer.

Patient: That’s a lot to process. What does this mean for me?

Doctor: Endometrial cancer means there are malignant cells in the lining of your uterus. The next step is to determine the type, grade, and stage of your cancer—this helps us decide on the best treatment plan and gives us an idea of your outlook.

Patient: What type and grade of endometrial cancer do I have?

Doctor: You have [type, e.g., endometrioid or serous] endometrial cancer, and the grade is [1, 2, or 3]. The grade tells us how aggressive the cancer cells look under the microscope.

Patient: Has my cancer spread? What stage is it?

Doctor: We use imaging and sometimes surgical findings to determine if the cancer has spread outside the uterus. The stage ranges from I (confined to the uterus) to IV (spread to distant organs). We’ll discuss your exact stage once all tests are complete.

Patient: What treatments might be right for me? What do you recommend?

Doctor: Treatment depends on the stage, grade, and your overall health. Most patients have surgery to remove the uterus, and sometimes the ovaries and lymph nodes. Radiation, chemotherapy, hormone therapy, or immunotherapy may be recommended depending on your specific case. We’ll tailor the plan to you.

Patient: What are the risks or side effects of these treatments?

Doctor: Surgery can cause pain, risk of infection, and, if the ovaries are removed, menopause. Radiation and chemotherapy can cause fatigue, digestive issues, and other side effects. Hormone and immunotherapies have their own risks. We’ll discuss these in detail and help you manage them.

Patient: Will treatment affect my sex life or ability to have children?

Doctor: Surgery usually means you won’t be able to have children. Some treatments may cause vaginal dryness or affect sexual function. We can discuss options for support and management.

Patient: What are the chances my cancer will come back?

Doctor: The risk depends on the stage, grade, and type of cancer, as well as the treatments you receive. We’ll discuss your individual risk and how we’ll monitor you after treatment.

Patient: Should I see a specialist or get a second opinion?

Doctor: It’s always reasonable to see a gynecologic oncologist or get a second opinion. Many patients do this, and it won’t affect your care. Your insurance often covers specialist visits, but we can check for you.

Patient: How will you support me during treatment?

Doctor: We’ll monitor your progress closely, help manage side effects, and connect you with support services. You can always bring a family member to appointments, take notes, or ask to record our discussions so you remember everything.

Patient: What should I do to get ready for treatment?

Doctor: We’ll review your overall health, discuss any other conditions you have, and make sure you’re as prepared as possible. Let us know about all medications and concerns you have.

Patient: What happens after treatment?

Doctor: After treatment, you’ll have regular follow-ups to check for recurrence and address any long-term effects. We’ll also talk about your quality of life, emotional well-being, and any other questions you have

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### 

### **OVARIAN CANCER**

### **DEFINITION AND DESCRIPTION**

### Ovarian cancer is a growth of cells that forms in the ovaries. The cells multiply quickly and can invade and destroy healthy body tissue.

### The female reproductive system contains two ovaries, one on each side of the uterus. The ovaries — each about the size of an almond — produce eggs (ova) as well as the hormones estrogen and progesterone.

### Ovarian cancer treatment usually involves surgery and chemotherapy.

### **Causes**

### It's not clear what causes ovarian cancer, though doctors have identified things that can increase the risk of the disease.

### Doctors know that ovarian cancer begins when cells in or near the ovaries develop changes (mutations) in their DNA. A cell's DNA contains the instructions that tell the cell what to do. The changes tell the cells to grow and multiply quickly, creating a mass (tumor) of cancer cells. The cancer cells continue living when healthy cells die. They can invade nearby tissues and break off from an initial tumor to spread (metastasize) to other parts of the body.

### Types of ovarian cancer

### The type of cell where the cancer begins determines the type of ovarian cancer you have and helps your doctor determine which treatments are best for you. Ovarian cancer types include:

### Epithelial ovarian cancer. This type is the most common. It includes several subtypes, including serous carcinoma and mucinous carcinoma.

### Stromal tumors. These rare tumors are usually diagnosed at an earlier stage than other ovarian cancers.

### Germ cell tumors. These rare ovarian cancers tend to occur at a younger age.

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### **Risk factors**

### Factors that can increase your risk of ovarian cancer include:

### Older age. The risk of ovarian cancer increases as you age. It's most often diagnosed in older adults.

### Inherited gene changes. A small percentage of ovarian cancers are caused by genes changes you inherit from your parents. The genes that increase the risk of ovarian cancer include *BRCA1* and *BRCA2*. These genes also increase the risk of breast cancer. Several other gene changes are known to increase the risk of ovarian cancer, including gene changes associated with Lynch syndrome and the genes *BRIP1*, *RAD51C* and *RAD51D*.

### Family history of ovarian cancer. If you have blood relatives who have been diagnosed with ovarian cancer, you may have an increased risk of the disease.

### Being overweight or obese. Being overweight or obese increases the risk of ovarian cancer.

### Postmenopausal hormone replacement therapy. Taking hormone replacement therapy to control menopause signs and symptoms may increase the risk of ovarian cancer.

### Endometriosis. Endometriosis is an often painful disorder in which tissue similar to the tissue that lines the inside of your uterus grows outside your uterus.

### Age when menstruation started and ended. Beginning menstruation at an early age or starting menopause at a later age, or both, may increase the risk of ovarian cancer.

### Never having been pregnant. If you've never been pregnant, you may have an increased risk of ovarian cancer.

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### **SYMPTOMS**

When ovarian cancer first develops, it might not cause any noticeable symptoms. When ovarian cancer symptoms happen, they're usually attributed to other, more common conditions.

Signs and symptoms of ovarian cancer may include:

* Abdominal bloating or swelling
* Quickly feeling full when eating
* Weight loss
* Discomfort in the pelvic area
* Fatigue
* Back pain
* Changes in bowel habits, such as constipation
* A frequent need to urinate

### 

### **When to see a doctor**

Make an appointment with your doctor if you have any signs or symptoms that worry you.

**DIAGNOSIS**

Tests and procedures used to diagnose ovarian cancer include:

* **Pelvic exam.** During a pelvic exam, your doctor inserts gloved fingers into your vagina and simultaneously presses a hand on your abdomen in order to feel (palpate) your pelvic organs. The doctor also visually examines your external genitalia, vagina and cervix.
* **Imaging tests.** Tests, such as ultrasound or CT scans of your abdomen and pelvis, may help determine the size, shape and structure of your ovaries.
* **Blood tests.** Blood tests might include organ function tests that can help determine your overall health.  
  Your doctor might also test your blood for tumor markers that indicate ovarian cancer. For example, a cancer antigen (CA) 125 test can detect a protein that's often found on the surface of ovarian cancer cells. These tests can't tell your doctor whether you have cancer, but they may provide clues about your diagnosis and prognosis.
* **Surgery.** Sometimes your doctor can't be certain of your diagnosis until you undergo surgery to remove an ovary and have it tested for signs of cancer.
* **Genetic testing.** Your doctor may recommend testing a sample of your blood to look for gene changes that increase the risk of ovarian cancer. Knowing you have an inherited change in your DNA helps your doctor make decisions about your treatment plan. You may wish to share the information with your blood relatives, such as your siblings and your children, since they also may have a risk of having those same gene changes.

Once it's confirmed that you have ovarian cancer, your doctor will use information from your tests and procedures to assign your cancer a stage. The stages of ovarian cancer range from 1 to 4, which are often indicated with Roman numerals I to IV. The lowest stage indicates that the cancer is confined to the ovaries. By stage 4, the cancer has spread to distant areas of the body.

**Treatment**

Treatment of ovarian cancer usually involves a combination of surgery and chemotherapy. Other treatments may be used in certain situations.

### **Surgery**

Operations to remove ovarian cancer include:

* **Surgery to remove one ovary.** For early-stage cancer that hasn't spread beyond one ovary, surgery may involve removing the affected ovary and its fallopian tube. This procedure may preserve your ability to have children.
* **Surgery to remove both ovaries.** If cancer is present in both your ovaries, but there are no signs of additional cancer, your surgeon may remove both ovaries and both fallopian tubes. This procedure leaves your uterus intact, so you may still be able to become pregnant using your own frozen embryos or eggs or with eggs from a donor.
* **Surgery to remove both ovaries and the uterus.** If your cancer is more extensive or if you don't wish to preserve your ability to have children, your surgeon will remove the ovaries, the fallopian tubes, the uterus, nearby lymph nodes and a fold of fatty abdominal tissue (omentum).
* **Surgery for advanced cancer.** If your cancer is advanced, your doctor may recommend surgery to remove as much of the cancer as possible. Sometimes chemotherapy is given before or after surgery in this situation.

### **Chemotherapy**

Chemotherapy is a drug treatment that uses chemicals to kill fast-growing cells in the body, including cancer cells. Chemotherapy drugs can be injected into a vein or taken by mouth.

Chemotherapy is often used after surgery to kill any cancer cells that might remain. It can also be used before surgery.

In certain situations, chemotherapy drugs may be heated and infused into the abdomen during surgery (hyperthermic intraperitoneal chemotherapy). The drugs are left in place for a certain amount of time before they're drained. Then the operation is completed.

### **Targeted therapy**

Targeted drug treatments focus on specific weaknesses present within cancer cells. By attacking these weaknesses, targeted drug treatments can cause cancer cells to die.

If you're considering targeted therapy for ovarian cancer, your doctor may test your cancer cells to determine which targeted therapy is most likely to have an effect on your cancer.

### **Hormone therapy**

Hormone therapy uses drugs to block the effects of the hormone estrogen on ovarian cancer cells. Some ovarian cancer cells use estrogen to help them grow, so blocking estrogen may help control the cancer.

Hormone therapy might be a treatment option for some types of slow-growing ovarian cancers. It may also be an option if the cancer comes back after initial treatments.

### **Immunotherapy**

Immunotherapy uses the immune system to fight cancer. The body's disease-fighting immune system may not attack cancer cells because they produce proteins that help them hide from the immune system cells. Immunotherapy works by interfering with that process.

Immunotherapy might be an option for treating ovarian cancer in certain situations.

### **Supportive (palliative) care**

Palliative care is specialized medical care that focuses on providing relief from pain and other symptoms of a serious illness. Palliative care specialists work with you, your family and your other doctors to provide an extra layer of support that complements your ongoing care. Palliative care can be used while undergoing other aggressive treatments, such as surgery and chemotherapy.

When palliative care is used along with all of the other appropriate treatments, people with cancer may feel better and live longer.

Palliative care is provided by a team of doctors, nurses and other specially trained professionals. Palliative care teams aim to improve the quality of life for people with cancer and their families. This form of care is offered alongside curative or other treatments you may be receiving.

## **Outlook / Prognosis**

After you’ve received ovarian cancer treatment, your healthcare provider will still see you for regular appointments. During these visits, they’ll check on any symptoms you may have and discuss any concerns. It’s important to pay close attention to your body and let your provider know if anything unusual is happening. Observation is key after ovarian cancer treatment.

### **What’s the ovarian cancer survival rate?**

The overall five-year survival rate for ovarian cancer is 49%. That means that approximately 49% of people diagnosed with ovarian cancer are alive five years from diagnosis.

It’s important to understand that survival rates are just estimates. They can’t tell you how long you’ll survive or predict the success of your treatment. If you have specific questions about ovarian cancer survival rates, talk with your healthcare provider.

**Prevention**

Symptoms and causes

There's no sure way to prevent ovarian cancer. But there may be ways to reduce your risk:

* **Consider taking birth control pills.** Ask your doctor whether birth control pills (oral contraceptives) may be right for you. Taking birth control pills reduces the risk of ovarian cancer. But these medications do have risks, so discuss whether the benefits outweigh those risks based on your situation.
* **Discuss your risk factors with your doctor.** If you have a family history of breast and ovarian cancers, bring this up with your doctor. Your doctor can determine what this may mean for your own risk of cancer. You may be referred to a genetic counselor who can help you decide whether genetic testing may be right for you. If you're found to have a gene change that increases your risk of ovarian cancer, you may consider surgery to remove your ovaries to prevent cancer.

## **Diagnostic Considerations**

## Ovarian cysts

### An ovarian cyst is a fluid-filled sac in an ovary. Ovarian cysts can develop from the neonatal period to postmenopause but most occur during infancy and adolescence, which are hormonally active periods of development. With the more frequent use of ultrasonography in recent years, the diagnosis of ovarian cysts has become more common.

### The normally functioning ovary produces a follicular cyst six to seven times each year. In most cases, these functional masses are self-limiting and resolve within the duration of a normal menstrual cycle. In rare situations, they persist longer or become enlarged. At this point, they represent a pathological condition.

## Evaluation of adnexal masses

### Adnexal masses present a diagnostic dilemma; the differential diagnosis is extensive, with most masses representing benign processes. [31, 32, 33] However, without histopathologic tissue diagnosis, a definitive diagnosis is generally precluded. Physicians must evaluate the likelihood of a pathologic process using clinical and radiologic information and balance the risk of surgical intervention for a benign versus malignant process.

### Since ovaries produce physiologic cysts in menstruating women, the likelihood of a benign process is higher. In contrast, the presence of an adnexal mass in prepubertal girls and postmenopausal women heightens the risk of a pathologic etiology.

### A review by Suh-Burgmann and Kinney suggests that surgical evaluation of adnexal masses is appropriate in the following circumstances:

### Symptomatic masses

### Masses associated with other signs of malignancy (eg, elevated cancer antigen 125 [CA125] levels in a postmenopausal patient, ascites)

### Women at high genetic risk for ovarian cancer

### Large masses (> 10 cm), which are less likely to regress, have a higher risk of symptoms, and are often more difficult to characterize on ultrasound

### Ultrasound features associated with malignancy include the following:

### Irregular solid tumor

### Ascites

### At least four papillary projections

### Irregular multilocular solid tumor ≥10 cm

### Very strong intratumoral blood flow

### 

## **Epidemiology**

In the United States, the age-adjusted incidence of ovarian cancer is 10.3 per 100,000 women per year, based on 2018–2022 cases. Ovarian cancer is more common in Whites than in Blacks (10.4 versus 9.2 cases per 100,000 women per year, respectively) and most common in American Indians/Alaska natives (11.4 cases per 100,000). Epithelial ovarian cancer can occur in girls as young as 15 years, but the median age at diagnosis is 63 years, and most cases are diagnosed in women 55-64 years of age. In the United States, the estimated lifetime risk is 1.1%.

The American Cancer Society estimates that 20,890 new cases of ovarian cancer will be diagnosed in 2025 and 12,730 women will die from the disease.Although ovarian cancer is the 18th most common cancer in women, it is the sixth most common cause of cancer death in women, accounting for 4% of cancer deaths.

From 2004 to 2021, the death rate from ovarian cancer decreased by an average of 2.4% each year.Median age at death is 71 years.

### International statistics

Internationally, ovarian cancer is the eighth most common cancer in women and the 18th most common cancer overall, with 324,603 new cases and 206,956 deaths in 2022.The worldwide age-standardized rate is 6.7 cases per 100,000. Currently, rates of ovarian cancer are falling in northern Europe and North America—regions that until the early 2000s had the highest age-standardized incidence—and are increasing in parts of eastern Europe and Asia. In 2022, the highest overall rate of ovarian cancer was in Latvia, with Samoa in second place.

Table. TNM and FIGO Classifications for Ovarian Cancer

| Primary tumor (T) | | |
| --- | --- | --- |
| *TNM* | *FIGO* |  |
| TX |  | Primary tumor cannot be assessed |
| T0 |  | No evidence of primary tumor |
| T1 | I | Tumor limited to the ovaries (one or both) |
| T1a | IA | Tumor limited to one ovary; capsule intact, no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings |
| T1b | IB | Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings |
| T1c | IC | Tumor limited to one or both ovaries with any of the subcategories below (IC1-3) |
| T1c1 | IC1 | Surgical spill |
| T1c2 | IC2 | Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface |
| T1c3 | IC3 | Malignant cells in ascites or peritoneal washings |
| T2 | II | Tumor involves one or both ovaries with pelvic extension below pelvic brim |
| T2a | IIA | Extension and/or implants on the uterus and/or tube(s) |
| T2b | IIB | Extension to and/or implants in other pelvic tissues |
| T3 | III | Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or retroperitoneal lymph node involvement |
| T3a | IIIA2 | Microscopic peritoneal metastasis beyond the pelvis with or without positive retroperitoneal lymph nodes |
| T3b | IIIB | Macroscopic peritoneal metastasis beyond the pelvis 2 cm or less in greatest dimension with or without positive retroperitoneal lymph nodes |
| T3c | IIIC | Macroscopic peritoneal metastasis beyond the pelvis >2 cm in greatest dimension including extension to liver capsule or spleen without parenchymal involvement of those organs and with or without positive retroperitoneal lymph nodes |
| Regional lymph nodes (N) | | |
| *TNM* | *FIGO* |  |
| NX |  | Regional lymph nodes cannot be assessed |
| N0 |  | No regional lymph node metastasis |
| N0(i+) |  | Isolated tumor cells in regional lymph node(s) ≤0.2 mm |
| N1 | IIIA1 | Positive (histologically confirmed) retroperitoneal lymph nodes |
| N1a | IIIAIi | Metastasis ≤10 mm in greatest dimension |
| N1b | IIIAIii | Metastasis more than 10 mm in greatest dimension |
| Distant metastasis (M) | | |
| *TNM* | *FIGO* |  |
| M0 |  | No distant metastasis |
| M1 | IV | Distant metastasis including cytology-positive pleural effusion; liver or splenic parenchymal involvement; extra-abdominal organ involvement including inguinal lymph nodes; transmural intestinal involvement |
| M1a | IVA | Pleural effusion with positive cytology |
| M1b | IVB | Liver or splenic parenchymal metastases; metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); transmural involvement of intestine |

### FIGO staging criteria for cancer of the ovary, fallopian tube, and peritoneum

FIGO staging criteria and equivalent TNM classifications are listed below. [4]

*Stage I*

Stage I (T1-N0-M0) consists of tumours limited to the ovaries or fallopian tubes.

Stage IA (T1a-N0-M0) includes the following:

* Tumor limited to one ovary (capsule intact) or fallopian tube
* No tumor on the external surface of the ovary or fallopian tube
* No malignant cells in ascites or peritoneal washings

Stage IB (T1b-N0-M0) includes the following:

* Tumor limited to both ovaries (capsules intact) or fallopian tubes
* No tumor on the external surface of the ovaries or fallopian tubes
* No malignant cells in ascites or peritoneal washings

Stage IC includes tumor limited to one or both ovaries or fallopian tubes, with any of the following:

* Stage IC1: (T1C1-N0-M0) Surgical spill
* Stage IC2: (T1C2-N0-M0) Capsule ruptured before surgery, or tumor on ovarian or fallopian tube surface
* Stage IC3: (T1C3-N0-M0) Malignant cells in the ascites or peritoneal washings

*Stage II*

In stage II (T2-N0-M0) tumor involves one or both ovaries or fallopian tubes, with pelvic extension (below pelvic brim) or primary peritoneal cancer .

* Stage IIA: (T2a-N0-M0) Extension and/or implants on the uterus and/or ovaries and/or fallopian tubes
* Stage IIB: (T2b-N0-M0) Extension to other pelvic intraperitoneal tissues

*Stage III*

In stage III, tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes (T1/T2-N1-M0).

Stage IIIA includes the following:

* Stage IIIA1: (T1/2-N1-M0) Positive (cytologically or histologically proven) retroperitoneal lymph nodes only
* Stage IIIA1(i) Metastasis up to 10 mm in greatest dimension
* Stage IIIA1(ii) Metastasis more than 10 mm in greatest dimension
* Stage IIIA2: (T3a2-N0/N1-M0) Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes

Stage IIIB (T3b-N0/N1-M0) involves macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes.

Stage IIIC (T3c-N0/N1-M0) involves macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes. Stage IIIC includes extension of tumor to the capsule of liver and spleen without parenchymal involvement of either organ.

*Stage IV*

Stage IV (any T–any N–M1) consists of distant metastasis, excluding peritoneal metastases, and includes the following:

* Stage IVA: Pleural effusion with positive cytology
* Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

## 

## **Chemotherapy agents**

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Cisplatin, carboplatin, and paclitaxel are chemotherapy agents approved for the initial treatment of ovarian cancer. Intrastrand cross-linking of DNA and inhibition of DNA precursors are among proposed mechanisms of action for platinum agents. The mechanism of action for paclitaxel is tubulin polymerization and microtubule stabilization.

Results from randomized studies have shown that platinum-containing regimens are superior to those that do not contain platinum. In addition, the combination of platinum and paclitaxel is superior to a regimen that does not include paclitaxel.

## Cisplatin (Platinol)

Indicated in established combination therapy in patients with metastatic ovarian tumors who have already received appropriate surgical and/or radiotherapeutic procedures. It also is indicated as secondary therapy in patients with metastatic ovarian tumors refractory to standard chemotherapy who have not previously received cisplatin therapy. For cisplatin, intrastrand cross-linking of DNA and inhibition of DNA precursors are among the proposed mechanisms of action.

## Carboplatin

For carboplatin, intrastrand cross-linking of DNA and inhibition of DNA precursors are among the proposed mechanisms of action.

## Paclitaxel (Taxol)

Indicated as subsequent therapy for the treatment of advanced carcinoma of the ovary. As first-line therapy, paclitaxel is indicated in combination with cisplatin. The mechanism of action of paclitaxel is tubulin polymerization and microtubule stabilization.

## Liposomal doxorubicin (Doxil)

Liposomal doxorubicin interferes with synthesis of nucleic acid by intercalating with DNA nucleotide pairs and topoisomerase II inhibition. Indicated for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy.

## **Antineoplastic Agents**

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Antineoplastic agents inhibit cell growth and proliferation. Several antineoplastic agents elicit a response in patients whose disease is resistant to platinum-based therapies. These include liposomal doxorubicin, topotecan, oral etoposide, gemcitabine, docetaxel, and vinorelbine. Other agents that may be used are ifosfamide, 5-fluorouracil with leucovorin, and altretamine (Hexalen).

## Etoposide

Etoposide is a glycosidic derivative of podophyllotoxin that exerts its cytotoxic effect through stabilization of the normally transient covalent intermediates formed between DNA substrate and topoisomerase II, leading to single- and double-strand DNA breaks.

## Topotecan (Hycamtin)

Topotecan binds to the topoisomerase I‑DNA complex and prevents religation of single-strand breaks. Indicated as monotherapy for the treatment of patients with metastatic ovarian cancer after disease progression on or after initial or subsequent chemotherapy.

## Gemcitabine (Gemzar)

Gemcitabine is a cytidine analog that is metabolized intracellularly to an active nucleotide. It inhibits ribonucleotide reductase and competes with deoxycytidine triphosphate for incorporation into DNA. It is indicated for advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy and is used in combination with carboplatin. It is cell-cycle specific for the S phase.

## Docetaxel (Taxotere)

Docetaxel is a semisynthetic taxane, a class of drugs that inhibits cancer cell growth by promoting assembly and blocking the disassembly of microtubules, thereby preventing cancer cell division, leading to cell death.

## Vinorelbine (Navelbine)

Vinorelbine is a semisynthetic vinca alkaloid that inhibits tubulin polymerization during G2 phase of cell division, thereby inhibiting mitosis.

## Ifosfamide

Ifosfamide inhibits DNA and protein synthesis and, thus, cell proliferation, by causing DNA cross-linking and denaturation of double helix.

## Fluorouracil (Adrucil)

Fluorouracil (5-FU) is a cycle-specific agent that has activity as single agent and, for many years, has been combined with biochemical modulator leucovorin. 5-FU inhibits tumor cell growth through at least 3 different mechanisms that ultimately disrupt DNA synthesis or cellular viability.

## Melphalan (Alkeran)

Melphalan inhibits mitosis by cross-linking DNA strands. Tablets are indicated for the palliation of nonresectable epithelial ovarian carcinoma.

## Altretamine (Hexalen

The mechanism of action of altretamine is unclear; reactive intermediates covalently bind to microsomal proteins and DNA, possibly causing DNA damage. Altretamine inhibits DNA and RNA synthesis by inhibiting the incorporation of radioactive thymidine and uridine into DNA and RNA. Indicated as palliative treatment of patients with persistent or recurrent ovarian cancer.

## Bevacizumab (Avastin)

Bevacizumab is a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF) receptors. Blocking the angiogenic VEGF receptor, in turn inhibits tumor angiogenesis, starving tumor of blood and nutrients. It is indicated in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent epithelial ovarian cancer in patients who received no more than 2 prior chemotherapy regimens. It is also indicated for women with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine chemotherapy, followed by bevacizumab alone.

## Mirvetuximab soravtansine (Elahere)

Indicated for women with FRα-positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received 1-3 prior systemic treatment regimens. Mirvetuximab soravtansine is an antibody-drug conjugate consisting of an anti-FRα antibody linked to maytansinoid DM4 (a tubulin-targeting agent).

## **PARP Inhibitors**

## 

Inhibition of poly (ADP-ribose) polymerase (PARP) enzymes result in disruption of cellular homeostasis and cell death.

## Olaparib (Lynparza)

Olaparib is an inhibitor of PARP enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular homeostasis (eg, DNA transcription, cell cycle regulation, DNA repair). Available as either tablets or capsules. The tablets and capsules are not interchangeable on a mg-to-mg basis due to differences in the dosing and bioavailability of each formulation, and therefore, should not be substituted with one another. The capsules and tablets are indicated as monotherapy for deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer in patients who have been treated with 3 or more prior lines of chemotherapy. Additionally, the tablets are approved for maintenance treatment of adults with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy. Discontinue bevacizumab before initiating maintenance therapy.

## Rucaparib (Rubraca)

By inhibiting PARP, rucaparib may cause increased formation of PARP-DNA complexes, resulting in DNA damage, apoptosis, and cell death. Increased cytotoxicity due to rucaparib was observed in tumor cell lines deficient in BRCA1/2 and other DNA repair genes. Indicated for monotherapy of women with deleterious BRCA mutation (germline and/or somatic) associated with advanced ovarian cancer who have been treated with ≥2 prior lines of chemotherapy. Also, indicated for the maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

## Niraparib (Zejula)

Niraparib is a highly selective for PARP-1 and PARP-2. PARP-1 and PARP-2 are involved in detecting DNA damage and promote repair. Inhibiting PARP enzymatic activity results in DNA damage, apoptosis and cell death. PARP inhibitor that is active both in patients with and those without BRCA mutations. Indicated for the maintenance treatment of adults with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Discontinue bevacizumab before initiating maintenance therapy.

## **Cytoprotective Agents**

## 

Mesna is indicated in the prevention of hemorrhagic cystitis in patients being treated with ifosfamide and cyclophosphamide.

## Mesna (Mesne

Mesna detoxifies metabolites of ifosfamide and cyclophosphamide. Usage is somewhat controversial, but it is commonly accepted that the total dose should be at least 60% of the total dose of the alkylating agent.

## **Antiemetics**

## 

Antiemetics are used for the prevention and treatment of nausea and vomiting associated with chemotherapy.

## Ondansetron (Zofran)

Ondansetron is a selective 5-HT3 receptor antagonist that blocks serotonin both peripherally and centrally. It prevents nausea and vomiting associated with emetogenic cancer chemotherapy (eg, high-dose cisplatin) and complete body radiotherapy.

## Granisetron (Kytril)

Granisetron is also a 5-HT3-receptor antagonist. It is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic chemotherapy, including high-dose cisplatin.

## Palonosetron (Aloxi)

Palonosetron is a selective 5-HT3 receptor antagonist with long half-life (40 h). It is indicated for the prevention and treatment of chemotherapy-induced nausea and vomiting. Palonosetron blocks 5-HT-3 receptors peripherally and centrally in the chemoreceptor trigger zone.

## Dexamethasone (Decadron)

Dexamethasone is used as an antiemetic in low doses during chemotherapy. It is usually employed in multiagent antiemetic regimens with 5HT-3 receptor antagonists.

## RAF/MEK Kinase Inhibitors

## Avutometinib (Avmapki)

MEK (mitogen-activated kinase)-1 inhibitor; induces formation of inactive RAF (rapidly accelerated fibrosarcoma)/MEK complexes and prevents phosphorylation of MEK1/2 by RAF. Inhibits proliferation of tumor cell lines that harbor KRAS mutations.

Indicated in combination with defactinib for treatment of KRAS-mutated recurrent low-grade serous ovarian cancer in adults who have received prior systemic therapy

## FAK Inhibitors

## Defactinib (Fakzynja)

Inhibitor of focal adhesion kinase (FAK) and proline-rich tyrosine kinase-2 (Pyk2). Indicated in combination with avutometinib for treatment of KRAS-mutated recurrent low-grade serous ovarian cancer in adults who have received prior systemic therapy

### **What questions should I ask my healthcare provider?**

What’s the location of the tumor?  
Your healthcare provider will determine the tumor's location using imaging tests (like ultrasound, CT, or MRI) and surgical findings. The tumor may be confined to the ovaries or involve other pelvic or abdominal organs, depending on the stage.

Has the cancer spread? If so, how far?  
The extent of spread (staging) is assessed through imaging and surgery. Early-stage cancer is limited to the ovaries, while advanced stages may involve the uterus, fallopian tubes, lymph nodes, or other abdominal organs. Tissue removed during surgery is tested to confirm the stage.

What treatments do you recommend?  
Treatment typically involves surgery to remove as much of the tumor as possible. This may be followed by chemotherapy, especially if the cancer is advanced. Targeted therapies and, in some cases, radiation therapy may also be recommended. Your treatment plan will be tailored to the cancer's type, stage, and your overall health.

How long will my treatment take?

* Surgery: Hospital stay is usually 3–7 days, with full recovery taking 6–12 weeks, depending on the extent of surgery and your health.
* Chemotherapy: Commonly given in 3–6 cycles, each lasting about 3–4 weeks, so the total duration is typically 3–6 months.
* Targeted therapy: May continue for up to 12 months or as long as it is effective.

Will I be able to work during my treatment?  
You may need to take 1–3 months off work to recover from surgery. Whether you can work during chemotherapy depends on your job and how you tolerate treatment. Fatigue is common, so a gradual return to work is often recommended. Discuss your specific situation with your healthcare team.

Are there ovarian cancer resources available?  
Yes, there are many resources for support and information:

* Cancer support groups and counseling services
* Patient information from organizations like Cancer Research UK, Ovarian Cancer Action, and local cancer centers
* Physiotherapists and specialist nurses for rehabilitation and recovery advice

**Subtype-Specific Genomic Alterations**

* Ovarian cancer includes several subtypes—most notably, high-grade serous carcinoma (HGSC) and non-HGSC types (such as endometrioid, clear cell, and mucinous tumors)—each with distinct genetic profiles.
* HGSC is characterized by nearly universal TP53 mutations, marking it as genomically unstable.
* Non-HGSC subtypes frequently harbor mutations in genes such as PIK3CA, ARID1A, and ATRX, with PIK3CA mutations particularly common in tumors of the PI3K/AKT/mTOR pathway.

Hereditary and Molecular Risk Factors

* Germline mutations in BRCA1 and BRCA2 are major contributors to hereditary ovarian cancer risk, with BRCA1 mutations especially linked to increased incidence.
* Other genetic factors under investigation include polymorphisms in the ESR1 gene (encoding the estrogen receptor ERα), which may serve as molecular markers for ovarian cancer, especially given the hormone-driven nature of the disease.

Metastatic and Prognostic Genomic Features

* Distinct mutation patterns are associated with metastatic behavior. For example, FLT3, CDH23, and EPAS1 mutations have been linked to specific metastatic routes and may influence prognosis.
* Molecular profiling can help stratify patients by subtype and metastatic risk, guiding more precise treatment strategies

## 

## **Ovarian Cancer Doctor-Patient Conversation**

Doctor:  
"Thank you for coming in today. I have reviewed your test results. The scans show a mass on your left ovary. Based on what we see, I recommend surgery to remove the tumor and confirm the diagnosis. After surgery, we’ll know more about whether the cancer has spread and what further treatment you might need."

Patient:  
"I’m feeling overwhelmed. Can you explain what this means for me?"

Doctor:  
"Of course. Ovarian cancer can be distressing, and it’s normal to feel this way. The most important thing right now is to gather as much information as possible. The surgery will help us understand the stage of the cancer—whether it’s confined to the ovary or has spread elsewhere. That information will guide our next steps."

Patient:  
"What kind of treatments might I need after surgery?"

Doctor:  
"That depends on what we find during surgery. If the cancer is early stage, surgery alone may be enough. If it has spread, chemotherapy is usually recommended. I’ll explain all the options once we have the full picture."

Patient:  
"How long will treatment take, and will I be able to work?"

Doctor:  
"Recovery from surgery can take several weeks. If chemotherapy is needed, it typically lasts about three to six months. Many people can work during treatment, but it depends on how you feel and the type of work you do. We’ll support you in making adjustments as needed."

Patient:  
"Are there resources or support groups I can contact?"

Doctor:  
"Yes, there are several organizations and support groups for ovarian cancer patients. I’ll give you a list and connect you with our nurse navigator, who can help you find the right resources."

Patient:  
"Thank you for explaining everything. I might have more questions later."

Doctor:  
"That’s completely fine. Write down any questions you think of, and bring them to our next appointment. You can also call or email me if something comes up before then. It’s important that you feel informed and supported throughout this process

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### **Epithelial ovarian cancer**

Epithelial ovarian cancer is the most common type of ovarian cancer. This cancer develops in the epithelial tissue, a thin lining that covers the outside of an ovary.

Cancer may also form in the lining of a fallopian tube. Or it can begin in the peritoneum, the tissue that covers your abdominal organs.

Medical experts consider fallopian tube cancers and primary peritoneal cancers to be epithelial ovarian cancers. The diseases share many similarities, including treatments.

#### **How common is epithelial ovarian cancer?**

Ovarian cancer is the second most common cancer that affects the female reproductive system (gynecological cancer). Uterine (endometrial) cancer is the most common. A female has a 1 in 78 lifetime risk of getting ovarian cancer.

In 2021, more than 21,400 people learned they had ovarian cancer. Epithelial ovarian cancer accounts for more than 9 in 10 of these cases. More than half of epithelial ovarian cancer cases affect people over 65.

#### **What are the types of epithelial ovarian cancer?**

About 3 out of 4 epithelial ovarian cancers are high-grade serous ovarian carcinomas (HGSOC). Cancer cells that are high-grade grow and spread faster than those that are low-grade.

Experts believe HGSOC grows slowly at first. It starts in your fallopian tubes. It may take up to six and a half years to reach your ovaries.

Once the cancer is in your ovaries, it spreads quickly. The cancer often affects your peritoneum and other parts of your body. Nearly 70% of HGSOCs are stage 3 or 4 at the time of diagnosis. This means the cancer has spread outside of the original tumor and is now metastatic cancer.

Less common types of epithelial ovarian cancers include:

* Endometrioid carcinoma: This cancer is more common in people who have endometriosis. It affects the endometrium, the inner lining of your uterus. It responds better to chemotherapy than some other types do.
* Low-grade serous ovarian carcinoma (LGSOC): This slow-growing cancer affects people at a younger age (between 45 and 57). It accounts for about 10% of epithelial ovarian cancers. The disease is often advanced at the time of diagnosis and doesn’t respond well to chemotherapy. Low-grade carcinomas grow slowly. They’re unlikely to become high-grade cancers.
* Mucinous carcinoma: These tumors are more distinct and respond well to treatments. They tend to be large (around 8 inches or 20 centimeters). Typically, they only affect your ovaries.
* Ovarian clear cell carcinoma (OCCC): People who are Asian and people with endometriosis are most at risk for this cancer. The disease is often advanced at diagnosis. It doesn’t respond well to chemotherapy.
* Primary squamous cell carcinoma (SCC) of the ovary: SCC typically develops from benign (noncancerous) conditions. It may form from ovarian cysts, endometriosis or Brenner tumors (solid, abnormal growths on your ovaries). It responds well to treatment when caught early.

## **Symptoms and Causes**

### **What causes epithelial ovarian cancer?**

Most cancers, including epithelial ovarian cancers, develop for no known reason. Research now suggests that many ovarian cancers actually start in cells at the end of the fallopian tubes. Then, they spread to the ovaries.

#### **Risk factors for epithelial ovarian cancer**

More than half of ovarian cancer diagnoses occur in people over 65 who have gone through menopause.

Certain factors may increase your risk of ovarian cancer, such as:

* Family history of ovarian cancer, breast cancer or colorectal (colon) cancer.
* Inheriting a change (mutation) to the BRCA gene.
* Inheriting a gene linked to family cancer syndromes like Lynch syndrome.
* Hormone therapy for menopause symptoms.
* Having a baby after age 35 or never having a full-term pregnancy.
* Carrying extra weight (obesity).

### **Symptoms of epithelial ovarian cancer**

Epithelial ovarian cancer rarely causes symptoms in its early stage. Symptoms become more noticeable as the disease progresses. As it spreads into your peritoneum (tissue that covers your abdominal organs), fluid accumulates in your abdomen (ascites).

You may also experience:

* Abdominal pain.
* Difficulty eating or feeling full quickly.
* Nausea and vomiting.
* Bloating.
* Pelvic pain.

Less common symptoms include:

* Urgent need to urinate (urge incontinence) or frequent urination (overactive bladder).
* Vaginal bleeding.

## **Diagnosis and Tests**

There aren’t any screening tests to detect ovarian cancer early. You might have tests only if you have symptoms or are high risk. Your healthcare provider may start by performing a pelvic exam to check for unusual growths or enlarged organs.

You might have a CA-125 blood test to check for elevated levels of a protein called cancer antigen 125 (CA-125). High levels may mean you need more testing.

These imaging tests help detect ovarian cancer:

* Transvaginal ultrasound.
* CT scan.
* MRI.
* Positron emission tomography (PET) scan.
* Chest X-rays (to look for metastatic cancer to the lungs).

You may also undergo a laparoscopy. This less invasive procedure lets your surgeon view your reproductive organs. Your healthcare provider may take tissue samples of a tumor to biopsy for cancer cells. A biopsy is the only way to definitively diagnose ovarian cancer.

### **Epithelial ovarian cancer stages**

Cancer staging helps healthcare providers track a cancer’s growth. It tells your healthcare provider if the cancer has spread and affects treatment decisions. The same tests that diagnose cancer can determine the cancer stage.

There are four stages of ovarian cancer. Some stages have sub-stages. A higher stage number reflects a more advanced cancer. Ovarian cancer stages include:

* Stage 1: Cancer is in one ovary or one fallopian tube.
* Stage 2: Cancer has spread to your uterus or your peritoneal cavity.
* Stage 3: Cancer has spread outside of your pelvis to other organs, lymph nodes or both.
* Stage 4: Cancer cells are in fluid surrounding your lungs, lymph nodes in your groin, organs or other parts of your body.

## **Management and Treatment**

Surgeons perform debulking surgery, which removes as much of the tumor as possible, followed by chemotherapy. Most people are initially cured, but the majority will get it again later.

People with early-stage cancer may choose to remove only the diseased ovary and fallopian tube.

People with advanced cancers often undergo debulking surgery to remove:

* Both fallopian tubes and ovaries (bilateral salpingo-oophorectomy).
* Uterus (hysterectomy).
* Omentum or fatty tissue covering your abdomen (omentectomy).
* Nearby lymph nodes.
* Any other diseased areas (like your small intestine, large intestine or spleen).

#### **Other epithelial ovarian cancer treatments**

Depending on the cancer type, you may get one or more of these treatments after surgery:

* Chemotherapy to kill cancer cells. Treatments include platinum compounds (carboplatin) and paclitaxel (Taxol®) or docetaxel (Taxotere®).
* Intraperitoneal chemotherapy to treat stage 3 ovarian cancer by injecting cisplatin and paclitaxel directly into your abdominal cavity through a surgically placed catheter (thin, hollow tube).
* Targeted therapies like bevacizumab (Avastin®) to stop cancer cells from growing and multiplying.
* Radiation therapy to destroy cancer cells with high-energy X-ray beams.

## **Outlook / Prognosis**

More than 13,000 people die from ovarian cancer every year. It’s the fifth leading cause of cancer deaths among women. But promising new treatments are under development in clinical trials. And researchers are making progress in detecting the disease earlier.

When epithelial ovarian cancer is detected before it spreads, the five-year survival rate is more than 90%. This number drops to about 30% when the cancer has spread (metastasized).

Many factors affect a cancer prognosis, including:

* Cancer has spread.
* Effectiveness of treatments.
* Location, size and number of tumors (cancer stage).

## **Prevention**

Studies show that people who take the pill (a form of hormonal birth control) for five or more years may cut their risk of ovarian cancer in half.

Certain surgical procedures may also lower cancer risk. Surgery to prevent cancer is called prophylactic surgery. This involves the removal of your fallopian tubes and ovaries with or without a hysterectomy. This is considered in people who are at high risk due to family history (like those who have a BRCA mutation or Lynch syndrome). However, experts advise taking these actions only if medically necessary. Removing your ovaries can bring on early menopause, which has its own effects on your body.

These procedures don’t completely eliminate cancer risk. Some people may already have undetected cancer when surgery takes place.

People with BRCA gene mutations can still get primary peritoneal cancer after removal of their fallopian tubes and ovaries. Ask your healthcare provider if you should have a BRCA test to find out if you have the BRCA gene.

### **When should I call the doctor?**

Call your healthcare provider if you experience:

* Changes in frequency or urgency of urination.
* Loss of appetite or feeling of fullness.
* Unexplained abdominal or pelvic pain.

#### **The differential diagnosis for ovarian cancer includes:**

#### Colon cancer

#### Embryologic remnants

#### Gastric adenocarcinoma

#### Metastatic gastrointestinal carcinoma

#### Ovarian torsion

#### Peritoneal cyst

#### Retroperitoneal mass

#### Uterine fibroids

#### Endometriosis

#### Papillary adenocarcinoma

#### Serous adenocarcinomas

#### Undifferentiated adenocarcinomas

#### Small-cell adenocarcinomas

#### Brenner tumors

#### **EPIDEMIOLOGY**

Study results have estimated the risk of a woman developing ovarian cancer in her lifetime up to age 95 to be 1.1%.In the US, in 2022, approximately more than 19,000 new ovarian cancers were diagnosed, and the number of ovarian cancer deaths was estimated to be more than 12,000. Furthermore, the incidence of ovarian cancer subtypes varies according to age. The incidence of high-grade serous ovarian cancer peaks in women between 60 and 65 years, and the incidence of low-grade endometroid ovarian cancer is highest in women between 45 and 50 years. Clear-cell ovarian cancers are highest in women between the ages of 55 and 60.The highest incidence of high-grade serous and low-grade endometrioid cancers is in non-Hispanic White women; Asian/Pacific Islander women have a higher incidence of clear cell cancer. Non-Hispanic Black women have the lowest incidence of all ovarian cancer subtypes.

Survival and recurrence rates also vary based on a patient's stage at diagnosis. More than half of patients diagnosed with ovarian cancer have metastasis at presentation. The 5-year survival of early-stage ovarian cancer is 93.1%, compared to 30.8% in advanced-stage disease. The recurrence risk in stage I ovarian cancer is less than 10%, while 90% of women with stage IV ovarian cancer have recurrence

## **Epithelial Ovarian Cancer: Procedures and Timelines**

## 1. Initial Diagnosis and Staging

* Procedures:
  + Imaging (ultrasound, CT, MRI)
  + Blood tests (CA125, HE4, others)
  + Surgical staging (exploratory laparotomy or laparoscopy)
* Timeline:
  + Usually completed within 1–2 weeks after suspicion or detection of a pelvic mass.

## 2. Primary Surgery

* Procedures:
  + Hysterectomy with bilateral salpingo-oophorectomy (removal of uterus, both ovaries, and fallopian tubes)
  + Omentectomy (removal of the fatty apron covering abdominal organs)
  + Lymph node sampling and peritoneal biopsies
  + Debulking (cytoreduction) to remove as much tumor as possible
* Timeline:
  + Surgery is typically scheduled promptly after diagnosis, often within 2–3 weeks.

## 3. Chemotherapy

* Standard Regimen:
  + Platinum-based doublet (carboplatin + paclitaxel)
  + Given intravenously every 3 weeks
  + Usually 3–6 cycles, depending on cancer stage and response
* Timeline:
  + Adjuvant chemotherapy usually starts 2–4 weeks after surgery, provided the patient has recovered adequately.
  + Each cycle lasts 3 weeks; total chemotherapy duration is about 3–5 months.

## 4. Neoadjuvant Chemotherapy (For Advanced Disease)

* Procedures:
  + 3–6 cycles of chemotherapy before surgery if optimal debulking is not initially possible
  + Followed by interval cytoreductive surgery, then additional chemotherapy cycles
* Timeline:
  + Neoadjuvant chemo: 9–18 weeks (3–6 cycles)
  + Surgery: Performed after initial chemo, then remaining cycles post-surgery

## 5. Targeted Therapy and Maintenance

* Indications:
  + For advanced or recurrent disease or specific genetic mutations (e.g., BRCA)
* Agents:
  + Bevacizumab (anti-angiogenic)
  + PARP inhibitors (olaparib, niraparib, rucaparib)
* Timeline:
  + Often started after completion of initial chemotherapy and continued as maintenance until progression or unacceptable toxicity.

## 6. Follow-Up and Surveillance

* Procedures:
  + Regular physical exams, imaging, and tumor marker monitoring
* Timeline:
  + Every 3–6 months for the first 2 years, then less frequently as time progresses

## **Genomic Data in Epithelial Ovarian Cancer**

Key Mutated Genes and Their Frequencies

* TP53: The most common mutation in epithelial ovarian cancer, especially in high-grade serous ovarian carcinoma (HGSOC), where it is present in up to 96–100% of cases. TP53 mutations are considered early driver events in tumor development and are associated with genomic instability.
* BRCA1/2: Germline or somatic mutations in BRCA1 or BRCA2 are found in 22–40% of HGSOC cases and are the most significant contributors to hereditary ovarian cancer. These mutations disrupt DNA repair via homologous recombination, increasing cancer risk and influencing treatment response.
* PIK3CA: Frequently mutated in ovarian clear cell carcinoma (OCCC, 51%) and endometrioid ovarian carcinoma (EnOC, 31.4%). Mutations in the PI3K/AKT pathway are more common in these subtypes than in HGSOC.
* KRAS: Commonly mutated in low-grade serous ovarian carcinoma (LGSOC, 54%) and mucinous ovarian carcinoma (up to 65%). KRAS mutations are rare in HGSOC.

Genomic Stratification and Clinical Implications

* Homologous Recombination Deficiency (HRD): Over half of HGSOCs show HRD, either due to BRCA1/2 mutations or other genetic/epigenetic changes. HRD status is clinically relevant for predicting response to PARP inhibitors and is assessed using specialized genomic tests.
* Other Genetic Syndromes: Lynch syndrome (associated with mismatch repair gene mutations) accounts for 10–15% of hereditary ovarian cancers and increases lifetime risk

#### **What should I ask my healthcare provider?**

## Should I have a BRCA test? Yes. Current guidelines recommend that all women diagnosed with invasive epithelial ovarian cancer should be offered genetic testing for BRCA1 and BRCA2, regardless of age, family history, or cancer subtype (except for mucinous tumors, which are less likely to be associated with BRCA mutations). Testing may involve both germline (inherited) and tumor (somatic) analysis, and should ideally be offered as early as possible after diagnosis. Knowing your BRCA status can impact your treatment options and inform your family’s risk.

## 

## What’s the best treatment for me? Treatment is individualized based on your cancer’s stage, subtype, genetic profile, and your overall health. Most patients with epithelial ovarian cancer undergo surgery to remove as much tumor as possible, followed by chemotherapy. If you have a BRCA mutation or homologous recombination deficiency, you may be eligible for targeted therapies such as PARP inhibitors. Your oncology team will tailor your treatment plan to maximize effectiveness and minimize side effects.

## 

## What are the treatment side effects? Common side effects of surgery include pain, fatigue, and risk of infection. Chemotherapy can cause nausea, hair loss, fatigue, increased infection risk, and neuropathy. Targeted therapies like PARP inhibitors may cause nausea, fatigue, anemia, and changes in blood counts. Your healthcare team will discuss ways to manage these side effects and monitor you closely throughout treatment.

## 

## Am I at risk for metastatic cancer? How can I lower this risk? Epithelial ovarian cancer can spread (metastasize), especially if diagnosed at a later stage. The risk of metastasis depends on the cancer’s stage, grade, and biology. Early and aggressive treatment (surgery and chemotherapy) is the best way to lower the risk of spread. BRCA testing can also guide the use of targeted therapies that may reduce the risk of recurrence and metastasis in eligible patients.

## 

## Should I look out for signs of complications? Yes. You should promptly report symptoms such as severe or persistent abdominal pain, bloating, shortness of breath, fever, heavy bleeding, or signs of infection. These could indicate complications from the cancer or its treatment. Your care team will provide detailed guidance on what to watch for and when to seek medical attention.

### What is the most aggressive form of ovarian cancer?

HGSOC (high-grade serous ovarian cancer) is a very aggressive ovarian cancer. The cancer grows slowly in your fallopian tubes at first. But it then spreads rapidly once it reaches your ovaries. Unfortunately, most people with HGSOC have advanced (metastatic) ovarian cancer by the time they get a diagnosis.

### Is it possible to have benign (noncancerous) epithelial ovarian tumors?

Yes. In fact, most epithelial ovarian tumors aren’t cancerous. Some tumors are borderline tumors or atypical proliferating tumors. They used to be known as low malignant potential tumors.

In borderline tumors, abnormal cells grow into the epithelial tissue but not your ovary’s supporting tissue (stroma). These cells usually stay in your ovary and rarely become cancer. When cancer occurs, 3 out of 4 cases are stage 1 (confined to your ovary and more treatable). These tumors tend to affect younger people.

## **Doctor-Patient Conversation for Epithelial Ovarian Cancer**

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Doctor:  
"Thank you for coming in today. I have reviewed your test results, and they show that you have epithelial ovarian cancer. I know this is difficult news, but I want you to know that we have a multidisciplinary team ready to support you through every step."

Patient:  
"What does this diagnosis mean for me? What are the next steps?"

Doctor:  
"The next step is to determine the exact stage of your cancer, which tells us how far it has spread. This usually involves surgery and possibly some additional imaging. After we have all the information, we’ll discuss the best treatment options. Most patients with this type of cancer will have surgery to remove as much of the tumor as possible, followed by chemotherapy. We’ll tailor the plan to your specific situation."

Patient:  
"Will I need any special tests?"

Doctor:  
"Yes, we recommend genetic testing for all patients with epithelial ovarian cancer, as certain inherited mutations, like BRCA1 and BRCA2, can affect your treatment plan and may be important for your family members as well."

Patient:  
"What kind of side effects should I expect from treatment?"

Doctor:  
"Surgery may cause some pain and require a few weeks of recovery. Chemotherapy can cause fatigue, nausea, hair loss, and increased risk of infection, but we have ways to help manage these side effects. We’ll discuss them in detail and support you throughout your treatment."

Patient:  
"Are there resources or support available for me?"

Doctor:  
"Absolutely. You’ll have access to a nurse navigator and a multidisciplinary team who can answer your questions, help with logistics like appointments and transportation, and connect you with support groups and counseling. We encourage you to participate in shared decision-making so your values and preferences are reflected in your care."

Patient:  
"How often will I need to come in for follow-up?"

Doctor:  
"After your initial treatment, you’ll have regular follow-up visits—every two to four months for the first two years, then every three to six months for the next three years. We’ll monitor for any signs of recurrence and address any concerns you may have

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[Epithelial Ovarian Cancer: Types, Stages, Symptoms & Causes](https://my.clevelandclinic.org/health/diseases/22250-epithelial-ovarian-cancer#overview)

**PROSTATE CANCER**

**DEFINITION AND DESCRIPTION**

Prostate cancer is a growth of cells that starts in the prostate. The prostate is a small gland that helps make semen. It's found just below the bladder. The prostate is part of the male reproductive system.

Prostate cancer is one of the most common types of cancer. Prostate cancer is usually found early, and it often grows slowly. Most people with prostate cancer are cured.

People diagnosed with early prostate cancer often have many treatment options to consider. It can feel overwhelming to learn about all the options and make a choice. Treatments may include surgery, radiation therapy or carefully watching the prostate cancer to see if it grows.

If the cancer grows beyond the prostate or if it spreads, there are still many treatment options. Prostate cancer that spreads can be more difficult to cure. But even when a cure isn't possible, treatments can slow the growth of the cancer and help you live longer.

**Symptoms**

Prostate cancer may not cause symptoms at first. Most prostate cancers are found at an early stage. This means that the cancer is only in the prostate. An early-stage prostate cancer often doesn't cause symptoms.

When they happen, early-stage prostate cancer signs and symptoms can include:

* Blood in the urine, which might make the urine look pink, red or cola-colored.
* Blood in the semen.
* Needing to urinate more often.
* Trouble getting started when trying to urinate.
* Waking up to urinate more often at night.

If the prostate cancer spreads, other symptoms can happen. Prostate cancer that spreads to other parts of the body is called metastatic prostate cancer. It also might be called stage 4 prostate cancer or advanced prostate cancer.

Signs and symptoms of advanced prostate cancer can include:

* Accidental leaking of urine.
* Back pain.
* Bone pain.
* Difficulty getting an erection, called erectile dysfunction.
* Feeling very tired.
* Losing weight without trying.
* Weakness in the arms or legs.

### 

### **When to see a doctor**

Make an appointment with a doctor or other healthcare professional if you have any symptoms that worry you.

**CAUSES**

It's often not clear what causes prostate cancer. Healthcare professionals have found some things that raise the risk of this cancer. These include older age, obesity and a family history of prostate cancer. The exact cause of prostate cancer often isn't known.

Prostate cancer starts when cells in the prostate develop changes in their DNA. A cell's DNA holds the instructions that tell the cell what to do. In healthy cells, the DNA tells the cells to grow and multiply at a set rate. The DNA also tells the cells to die at a set time.

In cancer cells, the DNA changes give different instructions. The changes tell the cancer cells to grow and multiply quickly. Cancer cells can keep living when healthy cells die. This causes too many cells.

The cancer cells might form a mass called a tumor. The tumor can grow to invade and destroy healthy body tissue. In time, cancer cells can break away and spread to other parts of the body. When cancer spreads, it's called metastatic cancer.

**Risk factors**

Factors that can increase the risk of prostate cancer include:

* **Older age.** The risk of prostate cancer goes up with age. It's most common after age 50.
* **Race and ethnicity.** In the United States, Black people have a greater risk of prostate cancer than do people of other races and ethnicities. Healthcare professionals aren't exactly sure why. In Black people, prostate cancer also is more likely to grow quickly or be advanced when detected.
* **Family history of prostate cancer.** If a blood relative, such as a parent or sibling, has been diagnosed with prostate cancer, your risk may be increased. The risk also may be increased if other close relatives have had prostate cancer. This includes your grandparents and your parents' siblings.
* **Family history of DNA changes.** Some DNA changes that increase the risk of cancer are passed from parents to children. The DNA changes called BRCA1 and BRCA2 can cause a higher risk of prostate cancer. These DNA changes are best known for increasing the risk of breast cancer and ovarian cancer.
* **Obesity.** People who have obesity may have a higher risk of prostate cancer compared with people considered to have a healthy weight. Studies of this issue have had mixed results. In people with obesity, prostate cancer is more likely to grow quickly and more likely to come back after treatment.
* **Smoking tobacco.** Some research shows a link between smoking and prostate cancer. But not all studies agree. People with prostate cancer who smoke may have a higher risk of the cancer coming back. People who smoke also have a higher risk of the cancer spreading beyond the prostate.

**Complications**

Complications of prostate cancer and its treatments include:

* **Cancer that spreads.** Prostate cancer can spread to other parts of the body, such as the bones or other organs. When prostate cancer spreads, it's called metastatic prostate cancer.
* **Incontinence.** Prostate cancer and its treatment can cause leaking of urine, also called urinary incontinence.
* **Erectile dysfunction.** Difficulty getting an erection is called erectile dysfunction. It can be caused by prostate cancer or its treatment.

**Prevention**

There is no sure way to prevent prostate cancer. You can help reduce your risk of prostate cancer if you:

* **Choose a healthy diet.** Eat a variety of fruits, vegetables and whole grains. Limit the amount of animal fats you eat. Fruits and vegetables contain many vitamins and nutrients that can do good for your health.  
  Foods that have been linked to a lower risk of prostate cancer include tomatoes, broccoli, cauliflower and soy. No studies have proved that these foods can prevent cancer. If you already enjoy eating these foods, there may be some added benefit in including them in your diet.
* **Exercise most days of the week.** It's not clear whether exercise can prevent prostate cancer. It may help you maintain a healthy weight. Exercise also may improve your overall health and your mood. Try to exercise most days of the week. If you're new to exercise, talk about it with a healthcare professional. Start slow and work your way up to more exercise time each day.
* **Maintain a healthy weight.** If your current weight is healthy, work to maintain it. Choose a healthy diet and exercise most days of the week. If you need to lose weight, add more exercise and eat fewer calories. Ask your healthcare professional for help creating a plan for healthy weight loss.
* **Don't smoke.** If you don't smoke, don't start. If you smoke, talk with a healthcare professional about what might help you quit. Medicines, nicotine replacement products and counseling can help.
* **Medicines to lower the risk of prostate cancer.** If you have a high risk of prostate cancer, you and your healthcare professional may consider medicines to lower the risk. These medicines include finasteride (Propecia, Proscar) and dutasteride (Avodart). They are most often used to treat prostate gland enlargement.  
  Ask your healthcare professional to talk about the benefits and risks of these medicines with you. When prostate cancer happens in people taking these medicines, it tends to grow faster. Your healthcare professional can help explain your risk and whether these medicines are right for you.

**DIAGNOSIS**

Prostate cancer diagnosis often starts with an exam and a blood test. A healthcare professional might do these tests as part of prostate cancer screening. Or you might have these tests if you have prostate cancer symptoms. If these first tests detect something concerning, imaging tests can make pictures of the prostate to look for signs of cancer. To be sure whether you have prostate cancer or not, a sample of prostate cells might be removed for testing.

### **Prostate cancer screening**

Prostate cancer screening tests look for prostate cancer in people who don't have any symptoms of the disease. Tests typically include a prostate-specific antigen blood test and a digital rectal exam.

Most experts recommend talking with your healthcare professional about prostate cancer screening around age 50. Together you can decide whether screening is right for you. You might consider starting the discussions sooner if you're a Black person, have a family history of prostate cancer or have other risk factors.

### **Digital rectal exam**

A digital rectal exam lets a healthcare professional examine the prostate. It's sometimes done as part of prostate cancer screening. It might be recommended if your symptoms lead your health professional to think you might have a prostate condition.

During a digital rectal exam, a healthcare professional inserts a gloved, lubricated finger into the rectum. The prostate is right by the rectum. The health professional feels the prostate for anything concerning in the texture, shape or size of the gland.

### **Prostate-specific antigen test**

A prostate-specific antigen test is a blood test that measures the amount of prostate-specific antigen in the blood. Prostate-specific antigen, also called PSA, is a substance that prostate cells make. Some PSA circulates in the blood. A PSA test detects the PSA in a blood sample.

Having a high level of PSA in your blood can be a sign of prostate cancer. But many other things also can cause a high PSA level, including prostate infection and prostate enlargement. If a PSA test detects an increased level of PSA in your blood, the test is usually repeated. Your healthcare professional might recommend doing the test again in a few weeks to see if the level goes down. If the level stays high, you might need an imaging test or a biopsy procedure to look for signs of cancer.

A PSA test is often used for prostate cancer screening. It also might be used if you have prostate cancer symptoms. The results can give your healthcare professional clues about your diagnosis.

### **Prostate ultrasound**

Ultrasound is an imaging test that uses sound waves to make pictures of the body. A prostate ultrasound makes pictures of the prostate. A healthcare professional might recommend this test if a digital rectal exam detects something concerning.

To get ultrasound pictures of the prostate, a healthcare professional puts a thin probe into the rectum. The probe uses sound waves to create a picture of the prostate gland. When an ultrasound is done this way, it's called a transrectal ultrasound.

### **Prostate MRI**

Magnetic resonance imaging, also called MRI, uses a magnetic field and radio waves to create pictures of the inside of the body. A prostate MRI makes pictures of the prostate. It's often used to look for concerning areas in the prostate that could be cancer.

Prostate MRI images may help your healthcare team decide whether you should have a biopsy procedure to remove prostate tissue for testing. The prostate MRI images also might help with planning the biopsy. If the MRI detects concerning areas in the prostate, the biopsy can target those areas.

During a prostate MRI, you lie on a table that goes into an MRI machine. Most MRI machines are large, tube-shaped magnets. The magnetic field inside the machine works with radio waves and hydrogen atoms in your body to create cross-sectional images.

Healthcare professionals use different kinds of MRI tests for prostate cancer, including:

* **Contrast-enhanced MRI.** A contrast-enhanced MRI scan uses a dye to make the pictures clearer. A healthcare professional puts the dye into a vein in your arm before the MRI.
* **MRI with endorectal coil.** MRI with endorectal coil uses a device inserted in the rectum to get better pictures of the prostate. Before this kind of MRI, a healthcare professional inserts a thin wire into your rectum. This thin wire, called an endorectal coil, sends signals to the MRI machine.
* **Multiparametric MRI.** A multiparametric MRI, also called mpMRI, tells the healthcare team more about the prostate tissue. This kind of MRI can help show the difference between healthy prostate tissue and prostate cancer.

### **Prostate biopsy**

A biopsy is a procedure to remove a sample of tissue for testing in a lab. A prostate biopsy involves removing tissue from the prostate. It's the only way to know for sure whether there is cancer in the prostate.

A prostate biopsy involves removing prostate tissue with a needle. The needle can go through the skin or through the rectum to get to the prostate. Your healthcare team chooses the kind of prostate biopsy that's best for you.

Types of prostate biopsy procedures include:

* **Transrectal prostate biopsy.** A transrectal prostate biopsy is a procedure to get a sample of prostate tissue. It involves putting a needle through the wall of the rectum and into the prostate. This is the most common type of prostate biopsy.  
  During this procedure, a healthcare professional inserts a thin probe into the rectum. The probe makes ultrasound pictures of the rectum. The probe also holds a needle. A healthcare professional uses ultrasound images to guide the needle. The needle goes through the rectum and into the prostate to remove tissue samples. Samples are removed from different parts of the prostate.
* **Perineal prostate biopsy.** A perineal prostate biopsy is a procedure to get a sample of prostate tissue. It involves putting a needle through the perineum and into the prostate. The perineum is the area of skin between the scrotum and the anus. This kind of prostate biopsy is less common.  
  During this procedure, a healthcare professional uses an imaging test to help guide the needle. Often this imaging test is an ultrasound. The health professional uses the needle to remove tissue from different parts of the prostate.

Prostate tissue samples go to a lab for testing. In the lab, tests can show whether samples contain cancer.

Prostate biopsy carries a risk of bleeding. Other side effects include blood in the urine and blood in the semen. Sometimes a prostate biopsy causes difficulty urinating or an infection. Side effects may depend on the procedure you have. Ask your healthcare team what you can expect as you recover.

### **Gleason score and grade group**

The Gleason score and grade group are numbers that tell your healthcare team whether your prostate cancer is growing slowly or quickly. How quickly a cancer grows also is called a cancer's grade.

To decide on the grade, doctors in the lab, called pathologists, look at the prostate cancer cells from a prostate biopsy. If the cancer cells look similar to healthy cells, then the cancer cells are low grade. Low-grade cancer grows slowly. If the cancer cells look very different from healthy cells, then the cancer cells are high grade. High-grade cancer grows quickly.

Prostate cancer grades range from 1 to 5. Grade 1 is a very low grade and grade 5 is a very high grade. To get the Gleason score, pathologists look at all the prostate biopsy samples to find the grade of each one. They figure out the most common grade found in the samples and the second most common grade. They add these two numbers together to get the Gleason score.

Gleason scores can range from 2 to 10. A score that's 5 or lower isn't considered cancer. Gleason scores from 6 to 10 are considered cancer. A Gleason score of 6 means the cancer is growing slowly. A Gleason score of 10 means the cancer is growing quickly.

Pathologists also report the prostate cancer grade as a group. The grade group is another way of stating how quickly the cancer cells are growing. The grade groups for prostate cancer are:

* **Grade group 1.** This means the Gleason score is 6 or less.
* **Grade group 2.** This means the Gleason score is 7. The most common grade in the prostate biopsy samples is 3. The second most common grade is 4.
* **Grade group 3.** This means the Gleason score is 7. The most common grade in the prostate biopsy samples is 4. The second most common grade is 3.
* **Grade group 4.** This means the Gleason score is 8.
* **Grade group 5.** This means the Gleason score is 9 or 10.

Your healthcare team uses your grade group to decide on your cancer's stage. The grade group also can help your care team plan your treatment.

### **Prostate cancer biomarker tests**

Biomarkers are things that can be detected in the body. Results from biomarker tests tell healthcare professionals about what's going on inside the body. Biomarker testing for cancer looks for biomarkers in the cancer cells. The results help healthcare professionals learn more about what's going on inside the cancer cells.

Healthcare professionals use prostate cancer biomarker tests to:

* **Decide whether to do a prostate biopsy.** Some prostate cancer biomarker tests use blood and urine samples to detect signals made by prostate cancer cells. The tests can tell your healthcare team whether a prostate biopsy is likely or not likely to find prostate cancer.
* **Decide on a treatment for early prostate cancer.** Some prostate cancer biomarker tests involve testing the cancer cells to see if the cancer has a high risk or a low risk of spreading beyond the prostate. If the results of other tests haven't been clear, this kind of test might help your care team understand your risk. The results can help decide between starting treatment right away or watching the cancer closely to see if it grows.
* **Decide on a treatment for advanced prostate cancer.** Other prostate cancer biomarker tests help when the cancer is advanced. For prostate cancer that has spread to other parts of the body, the results of these tests can tell your healthcare team whether certain treatments are likely to work on your cancer cells. For this kind of test, your healthcare team may test some of the cells that have spread. The cells might be removed with a biopsy procedure or collected from a blood sample.

Not everyone needs a prostate cancer biomarker test. These tests are new, and healthcare professionals are still deciding how best to use them.

### **Imaging tests to look for prostate cancer that has spread**

Imaging tests can look for signs that the cancer has spread beyond the prostate. These tests might detect cancer that has spread to the lymph nodes or to other parts of the body.

Most people with prostate cancer only have cancer in the prostate. They might not need these other imaging tests to look for signs of cancer spread. Ask your healthcare team whether you need these imaging tests.

When prostate cancer spreads beyond the prostate, it might be called metastatic prostate cancer, stage 4 prostate cancer or advanced prostate cancer. Imaging tests used to detect this kind of prostate cancer include:

* **A bone scan.** A bone scan uses nuclear imaging to make pictures. Nuclear imaging involves using small amounts of radioactive substances, called radioactive tracers. A special camera that can detect the radioactivity also is used along with a computer. The tracer is absorbed more by cells and tissues that are changing. Cancer cells are often growing and changing quickly. Bone scan images can detect places in the bones that absorb the tracer. These may be signs of prostate cancer in the bones.
* **A computerized tomography scan.** A computerized tomography scan, also called a CT scan, is a type of imaging that uses X-ray techniques to create detailed images of the body. It then uses a computer to create cross-sectional images, also called slices, of the bones, blood vessels and soft tissues inside the body. A CT scan can detect prostate cancer that has spread to the lymph nodes or other places in the body.
* **Magnetic resonance imaging.** Magnetic resonance imaging, also called MRI, uses a magnetic field and radio waves to create pictures of the inside of the body. An MRI can detect prostate cancer that has spread to the lymph nodes or other places in the body.
* **A positron emission tomography scan.** A positron emission tomography scan, also called a PET scan, is a nuclear imaging test. It uses a radioactive tracer that's injected into a vein. The tracer contains a substance that helps it stick to fast-growing cells, such as cancer cells. The PET images show the places where the tracer builds up. A PET scan can detect prostate cancer that has spread to other places in the body.
* **A prostate-specific membrane antigen PET scan.** A prostate-specific membrane antigen PET scan also is called a PSMA PET scan. Like other PET scans, this test uses a radioactive tracer. The tracer contains a substance that helps the tracer stick to prostate cancer cells. The substance attaches to a protein that's found on the surface of prostate cancer cells. A PSMA PET scan can detect prostate cancer that has spread to the lymph nodes or other places in the body.

### **Prostate cancer stages**

Your healthcare team uses the results of your tests and procedures to give your cancer a stage. The cancer's stage tells your healthcare team about the size of the cancer and how quickly it's growing.

To decide your prostate cancer stage, your healthcare team uses these factors:

* How much of the prostate contains cancer.
* Whether the cancer has grown beyond the prostate, such as into the rectum, bladder or other nearby areas.
* Whether the cancer has spread to the lymph nodes.
* Whether the cancer has spread to other parts of the body, such as the bones.
* The level of PSA in the blood.
* The grade group.

Prostate cancer stages range from 1 to 4. A lower number means the cancer is small and only in the prostate. A lower number stage typically means the cancer is very likely to be cured. If the cancer grows larger or spreads, the stage goes up. A higher number stage may mean a cure is less likely. Your prognosis depends on many factors, so talk about this with your healthcare team.

The stages of prostate cancer are:

* **Stage 1 prostate cancer.** A stage 1 prostate cancer means the cancer is small and only in the prostate. The cancer only affects one side of the prostate gland. The PSA level is low and the grade group is 1.
* **Stage 2A prostate cancer.** A stage 2A prostate cancer may be a small cancer that only affects one side of the prostate, but the PSA level is intermediate. This stage also can mean that the cancer affects both sides of the prostate, but the PSA level is low. At this stage, the grade group is 1.
* **Stage 2B prostate cancer.** A stage 2B prostate cancer is only in the prostate. The cancer may have grown to involve both sides of the prostate gland. At this stage, the PSA level is intermediate. The grade group is 2.
* **Stage 2C prostate cancer.** A stage 2C prostate cancer is only in the prostate. The cancer may have grown to involve both sides of the prostate gland. The PSA level is intermediate. The grade group is 3 or 4.
* **Stage 3A prostate cancer.** A stage 3A prostate cancer is only in the prostate. The cancer may have grown to involve both sides of the prostate gland. The PSA level is high. This stage includes grade groups 1 to 4.
* **Stage 3B prostate cancer.** A stage 3B prostate cancer has grown beyond the prostate. The cancer might extend to the seminal vesicles, bladder, rectum or other nearby organs. The PSA level may be low, intermediate or high. This stage includes grade groups 1 to 4.
* **Stage 3C prostate cancer.** A stage 3C prostate cancer has a grade group of 5. It includes any size of prostate cancer. The cancer may have grown beyond the prostate, but it hasn't spread yet.
* **Stage 4A prostate cancer.** A stage 4A prostate cancer has spread to the lymph nodes.
* **Stage 4B prostate cancer.** A stage 4B prostate cancer has spread to other parts of the body, such as the bones.

### **Prostate cancer prognosis**

The cancer prognosis tells you how likely it is that the cancer can be cured. Your healthcare team can get a general sense of your outlook using your prostate cancer stage. But the stage can't tell your future. Your personal prognosis may depend on:

* Your age.
* Your overall health.
* The cancer's stage.
* PSA test results.
* Prostate biopsy results.
* Grade group.

Talk with your healthcare team about your prognosis if you want to know what to expect. Your healthcare team can explain what they consider when thinking about your prognosis.

### **Prostate cancer survival rates**

The chance of surviving prostate cancer is quite good for most people. To understand prostate cancer survival rates, experts study many people with prostate cancer to see how many are living five years after their diagnosis.

When the cancer is only in the prostate, the chance of surviving at least five years is 100%. As the cancer spreads beyond the prostate, the chances get lower. When prostate cancer has spread to other parts of the body, called metastatic prostate cancer, the chances of surviving at least five years is about 37%.

Keep in mind that survival statistics take five years to collect. The most recent survival rates include people who had prostate cancer treatment more than five years ago. These people may not have had access to the latest treatments. Over the last few decades, prostate cancer death rates have been falling and survival rates have been increasing.

**Treatment**

Prostate cancer treatments include surgery, radiation therapy and medicines. Medicines for prostate cancer include hormone therapy, chemotherapy, targeted therapy and immunotherapy. Sometimes other treatments are used to treat prostate cancer. These might include having ablation therapy with heat or cold to hurt the cancer cells and receiving medicine that gives radiation directly to the cancer cells.

Your healthcare team considers many things when creating your prostate cancer treatment plan. They consider the size of your cancer, whether it has spread and how quickly it's growing. They also consider your overall health and your preferences. Talk with your healthcare team about your options.

### **Active surveillance for prostate cancer**

Prostate cancer treatment isn't always needed right away. Instead, the healthcare team may watch the cancer closely. Healthcare professionals call this active surveillance. It often involves regular follow-up blood tests, imaging tests and prostate biopsies. If tests show that the cancer is growing, you may choose to start treatment. For some prostate cancers, treatment may never be needed.

Active surveillance may be an option for prostate cancer that doesn't cause symptoms and is expected to grow very slowly. Active surveillance may be right for someone who has another serious health condition that makes cancer treatment more difficult.

Surgery for prostate cancer most often involves removing the prostate. Surgery to remove the prostate is called prostatectomy. It's often used when the cancer is only in the prostate. Sometimes it can treat a cancer that grows larger or spreads to the lymph nodes.

There are many ways of doing a prostatectomy for prostate cancer, including:

* **Laparoscopic prostatectomy.** During a laparoscopic prostatectomy for prostate cancer, a surgeon makes several small cuts in the belly. The surgeon puts surgical tools through the cuts. The surgeon uses the tools to remove the prostate.
* **Robotic prostatectomy.** During a robotic prostatectomy for prostate cancer, a surgeon uses hand controls to guide robotic arms. The arms hold the surgical tools. The surgeon sits at a console to use the hand controls that move the robotic arms. Just like in a laparoscopic prostatectomy, the surgeon makes several small cuts in the belly. The surgeon guides the robotic arms to put surgical tools through the cuts in the belly to remove the prostate. Most prostate cancer operations use robotic prostatectomy.
* **Open prostatectomy.** During open prostatectomy for prostate cancer, a surgeon makes one large cut in the lower belly. The surgeon removes the prostate through this large cut. This procedure also is called retropubic prostatectomy. This way of doing prostate cancer surgery is not very common. But it might be the right choice in some situations.

Prostate cancer surgery carries a risk of bleeding, infection, pain and blood clots. If they happen, these complications tend to occur soon after surgery. Laparoscopic prostatectomy and robotic prostatectomy tend to have a lower risk of these side effects.

Long term, prostate cancer surgery can cause leaking urine, called urinary incontinence. It also can cause difficulty getting an erection, called erectile dysfunction. These side effects usually get better over time.

### **External beam radiation therapy for prostate cancer**

Radiation therapy treats cancer with powerful energy beams. External beam radiation is one type of radiation therapy used for prostate cancer. It involves using a machine to aim beams of radiation at the body.

During external beam radiation therapy, you lie on a table while a machine moves around your body. The machine directs powerful energy beams to prostate cancer. The beams can be made of X-rays, protons or other types of energy.

You typically have external beam radiation treatments five days a week for several weeks. Some medical centers offer shorter radiation therapy treatment schedules. This approach uses a similar dose of radiation but spreads the dose over fewer days. Some radiation therapy treatments happen over a few days.

Healthcare professionals use external beam radiation to treat cancer that's only in the prostate. For a small prostate cancer, it might be the only treatment needed.

Sometimes healthcare professionals recommend external beam radiation after surgery. The radiation can help kill any cancer cells that might remain. It can lower the risk that the cancer could spread or come back.

External beam radiation also helps with advanced prostate cancer. When the cancer spreads to other parts of the body, such as the bones, the radiation can slow the cancer's growth. Radiation also can help with symptoms, such as pain.

External beam radiation therapy for prostate cancer can cause side effects such as irritation of the intestines. This can cause diarrhea, bloody stool and a feeling that the bowel can't be emptied completely. Other side effects include frequent urination, painful urination and difficulty starting urination. After treatment, there also can be difficulty getting an erection.

### **Brachytherapy for prostate cancer**

Brachytherapy involves placing radiation inside the body. Brachytherapy is one type of radiation therapy used to treat prostate cancer.

Most prostate cancer brachytherapy treatments are permanent. Permanent brachytherapy is sometimes called low dose rate brachytherapy. This treatment uses rice-sized seeds that contain radioactive material. A healthcare professional uses a device to insert the seeds into the prostate gland. The seeds slowly give off a low dose of radiation over time.

Sometimes prostate cancer brachytherapy treatments are temporary. Temporary brachytherapy is sometimes called high dose rate brachytherapy. This treatment involves placing radioactive material in the prostate for a short period. Then the radioactive material is removed. The treatment might repeat over multiple days.

Healthcare professionals use brachytherapy to treat prostate cancer that's only in the prostate. Brachytherapy doesn't treat cancer that has spread to other parts of the body.

Side effects of brachytherapy for prostate cancer include frequent urination, painful urination and blood in the urine. There may be diarrhea, constipation and a feeling that the bowel can't be emptied completely. There also can be difficulty getting an erection.

### **Ablation therapy for prostate cancer**

Ablation is a procedure that applies treatment directly to the cancer cells in order to hurt them. It's not a standard treatment for prostate cancer but is used in some situations. Types of ablation therapy used for prostate cancer include:

* **Cryoablation for prostate cancer.** Cryoablation uses cold to hurt cancer cells. It's also called cryotherapy. To treat prostate cancer, a healthcare professional inserts thin needles through the skin of the perineum. The needles go through the skin and into the prostate. The health professional uses a machine to cool down the needles. This causes the tissue around the needles to freeze. The health professional carefully controls how much of the prostate gets the freezing treatment. Then the health professional allows the tissue to thaw. The freezing and thawing hurts the cancer cells.
* **High-intensity focused ultrasound for prostate cancer.** High-intensity focused ultrasound treatment, also called HIFU, uses heat to hurt the cancer cells. The heat comes from high-intensity sound waves, called ultrasound waves. To treat the prostate, a healthcare professional inserts a thin probe into the rectum. The probe sends out ultrasound waves to the prostate. This causes the tissue to heat up to a temperature that hurts the cancer cells.

Healthcare professionals sometimes use ablation therapy to treat very small prostate cancers. It might be used when surgery isn't possible. For example, ablation may be the best choice if other health conditions make surgery and other treatments risky.

Healthcare professionals sometimes use ablation therapy if the cancer comes back. It might help treat prostate cancer that comes back after radiation therapy.

Ablation therapy side effects include pain and swelling in the treatment area and difficulty getting an erection. Sometimes the treatment can hurt the bladder or the tube that carries urine out of the bladder, called the urethra. This may lead to using urinary catheters to help with urination.

### **Hormone therapy for prostate cancer**

Hormone therapy for prostate cancer is a treatment that stops the hormone testosterone either from being made or from reaching prostate cancer cells. Prostate cancer cells rely on testosterone to help them grow. Cutting off the supply of testosterone may cause cancer cells to die or to grow more slowly.

Hormone therapy treatments for prostate cancer include:

* **Medicines that stop the testicles from making testosterone.** Some medicines stop cells from getting the signals that tell them to make testosterone. These medicines are called luteinizing hormone-releasing hormone agonists and antagonists. Another name for these medicines is LHRH agonists and antagonists. Medicines that work in this way include goserelin (Zoladex) and degarelix (Firmagon), among many others.
* **Medicines that stop testosterone from acting on cancer cells.** These medicines, known as antiandrogens, are often used with LHRH agonists. That's because LHRH agonists can cause a brief rise in testosterone levels before testosterone levels go down. Medicines that work in this way include bicalutamide (Casodex) and nilutamide (Nilandron), among many others.
* **Surgery to remove the testicles, called orchiectomy.** Surgery to remove both testicles lowers testosterone levels in the body quickly.

Hormone therapy is often used to treat prostate cancer that has spread to the lymph nodes or to other parts of the body. Hormone therapy can shrink the cancer and slow its growth.

Hormone therapy is sometimes used with radiation therapy to treat cancer that hasn't spread beyond the prostate. It helps make the radiation therapy more effective.

Side effects of prostate cancer hormone therapy include hot flashes, trouble sleeping, loss of muscle and increase in body fat. There may be a loss of sex drive, and it can be more difficult to get an erection. Other hormone therapy risks include an increased chance of getting diabetes and heart disease.

### **Chemotherapy for prostate cancer**

Chemotherapy treats cancer with strong medicines. Chemotherapy medicines are sometimes used with hormone therapy medicines for prostate cancer. Healthcare professionals sometimes use these medicines together for advanced prostate cancer that has spread to the lymph nodes or to other parts of the body. Chemotherapy also helps treat advanced prostate cancer when hormone therapy isn't working.

Chemotherapy medicines commonly used for prostate cancer include docetaxel (Beizray, Docivyx, Taxotere) and cabazitaxel (Jevtana). A healthcare professional gives these medicines through a vein. The treatments typically happen once every three weeks. Side effects of these medicines include feeling very tired, easy bruising and more-frequent infections. They also can damage the nerves in the fingers and toes, called peripheral neuropathy. This can cause numbness and tingling in the fingers and toes.

Other chemotherapy medicines exist. Your healthcare team picks the best medicines for your cancer.

### **Targeted therapy for prostate cancer**

Targeted therapy for cancer is a treatment that uses medicines that attack specific chemicals in the cancer cells. By blocking these chemicals, targeted treatments can cause cancer cells to die.

For prostate cancer, targeted therapy medicines can help treat cancer that spreads or that comes back after other treatments. Healthcare teams often give targeted therapy medicines with hormone therapy medicines. Sometimes targeted therapy medicines are used alone.

Many **targeted therapy medicines** exist. Targeted therapy medicines sometimes used for prostate cancer include:

* Niraparib (Zejula).
* Olaparib (Lynparza).
* Rucaparib (Rubraca).
* Talazoparib (Talzenna).

These targeted therapy medicines come as a pill or capsule you swallow. The medicines block the action of enzymes in the cancer cells that help repair breaks in the DNA. These targeted therapy medicines only work in people with certain DNA changes in their cells. To find out if these changes are present in your cells, your healthcare team may test your blood or some of your cancer cells.

**Side effects of targeted therapy medicines** for prostate cancer include feeling very tired, nausea and loss of appetite. Other side effects include diarrhea, cough, easy bruising and more-frequent infections.

### **Immunotherapy for prostate cancer**

Immunotherapy for cancer is a treatment with medicine that helps the body's immune system kill cancer cells. The immune system fights off diseases by attacking germs and other cells that shouldn't be in the body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells.

Prostate cancer immunotherapy can involve:

* **Cell therapy for prostate cancer.** Cell therapy is a treatment that trains immune system cells to find and stop cancer cells. It involves taking some of your immune system cells from your blood. The cells go to a lab where they get treatment that helps them find prostate cancer cells. The treated cells are put back in your body where they can fight the cancer. One treatment that works in this way is sipuleucel-T (Provenge). It can cause flu-like side effects, such as fever, chills and headache.
* **Immune checkpoint inhibitors for prostate cancer.** Immunotherapy medicines called immune checkpoint inhibitors help immune system cells find cancer cells. Some cells can send signals called immune checkpoints to the immune system. Immune checkpoints tell the immune system cells not to attack. Usually, immune checkpoints help keep the immune system from hurting healthy cells. But some cancer cells also send these signals. Immune checkpoint inhibitor medicines stop cancer cells from sending the signals to not attack.  
  These medicines only work in people with cancer cells that have certain DNA changes. Most prostate cancers don't respond to this treatment. One example of an immune checkpoint inhibitor used for prostate cancer is pembrolizumab (Keytruda). Side effects can include feeling very tired, itchy skin, diarrhea, loss of appetite and rash. Sometimes this treatment causes the immune system to attack the organs, leading to serious complications.

Healthcare professionals sometimes use prostate cancer immunotherapy treatments for cancer that has spread to other parts of the body, called metastatic prostate cancer.

### **Radiopharmaceutical treatments for prostate cancer**

Radiopharmaceutical treatments are medicines that contain a radioactive substance. Radiopharmaceutical treatments used for cancer can deliver radiation to cancer cells.

For prostate cancer, radiopharmaceutical treatments are typically used when the cancer is advanced. People with stage 4 prostate cancer that has spread to other parts of the body, also called metastatic prostate cancer, might consider radiopharmaceutical treatments.

Radiopharmaceuticals used for prostate cancer include:

* **Treatments that target PSMA.** Radiopharmaceutical treatments can target a protein that's common on prostate cancer cells called prostate-specific membrane antigen. It's also called PSMA. One radiopharmaceutical medicine that works in this way is lutetium Lu-177 vipivotide tetraxetan (Pluvicto). This medicine contains a molecule that finds and sticks to the PSMA on prostate cancer cells. The medicine also contains a radioactive substance. A healthcare professional gives this medicine through a vein. The medicine finds the prostate cancer cells and releases the radiation directly into the cells. PSMA therapy can treat prostate cancer anywhere in the body. This treatment only works if the prostate cancer cells make the PSMA protein. Side effects include dry mouth, nausea and feeling very tired.
* **Treatments that target the bones.** Some radiopharmaceutical medicines contain a radioactive substance that is attracted to bones. When a healthcare professional puts this medicine into a vein, it travels to the bones and releases the radiation. One medicine that works in this way is radium Ra-223 (Xofigo). Healthcare professionals sometimes use it when prostate cancer spreads to the bones but not to other parts of the body. This treatment can help with bone pain and other symptoms. Side effects include diarrhea and feeling very tired.

**Alternative medicine**

No complementary or alternative treatments will cure prostate cancer. However, complementary and alternative prostate cancer treatments may help you cope with the side effects of cancer and its treatment.

Many people with cancer experience distress at some point. If you're distressed, you may feel sad, angry or anxious. You may have difficulty sleeping or find yourself constantly thinking about your cancer.

Several complementary medicine techniques may help you cope with distress, including:

* Art therapy.
* Dance or movement therapy.
* Exercise.
* Meditation.
* Music therapy.
* Relaxation techniques.
* Spiritual practices.

Talk with your healthcare team if you're feeling distress. Some things that cause distress are treated with medicines and other treatments. If you're interested in trying complementary treatments, talk about them with your healthcare team to make sure they are safe for you.

## **QUESTION AND ANSWER SET**

## Do I have prostate cancer?

A diagnosis of prostate cancer is confirmed by a prostate biopsy, which examines tissue samples under a microscope. If your biopsy shows cancerous cells, your doctor will explain the grade and extent of the cancer.

## How large is my prostate cancer?

The size and extent are assessed by imaging (MRI, CT, or ultrasound) and by examining how many biopsy samples contain cancer and how much of each sample is involved. This helps determine if the cancer is confined to the prostate or has spread.

## Has my prostate cancer spread beyond my prostate?

To determine if the cancer has spread, your doctor will consider imaging results, your PSA level, and the Gleason score. Additional scans (such as bone scans or CT) may be ordered if there are signs of more advanced disease or if your PSA or Gleason score is high.

## What's my Gleason score?

The Gleason score is a grading system that reflects how aggressive your prostate cancer is. It is calculated by adding the two most common patterns seen in your biopsy samples, each graded from 3 to 5. Scores range from 6 (least aggressive) to 10 (most aggressive). The Gleason score helps predict how quickly the cancer might grow and spread.

## What's my prostate-specific antigen (PSA) level?

PSA is a protein produced by the prostate, measured in your blood. Higher PSA levels can indicate a higher chance of prostate cancer or more advanced disease. PSA is used alongside other findings to guide diagnosis and treatment decisions. A PSA below 4 ng/mL is generally considered low risk, while higher levels increase the likelihood of cancer.

## Will I need more tests?

You may need additional imaging or blood tests to determine the stage of your cancer and whether it has spread. The need for more tests depends on your PSA, Gleason score, and physical exam findings.

## What are my treatment options?

Treatment options include:

* Active surveillance (monitoring)
* Surgery (prostatectomy)
* Radiation therapy
* Hormone therapy
* Chemotherapy (for advanced cases)  
  The best option depends on your cancer’s stage, grade, PSA, overall health, and personal preferences.

## Is there one treatment option you think is best for me?

Your doctor will recommend a treatment based on your specific cancer characteristics and health status. For low-risk, slow-growing cancers, active surveillance may be appropriate. For higher-risk or more aggressive cancers, surgery or radiation may be recommended.

## Do I need cancer treatment right away, or is it possible to wait and see if the cancer grows?

If your cancer is low grade (Gleason 6), low PSA, and confined to the prostate, active surveillance may be an option, allowing you to delay or avoid treatment unless the cancer progresses. More aggressive cancers usually require prompt treatment.

## What are the potential side effects of each treatment?

* Surgery: Urinary incontinence, erectile dysfunction, surgical risks.
* Radiation: Urinary symptoms, bowel changes, erectile dysfunction.
* Hormone therapy: Hot flashes, loss of libido, bone thinning, fatigue.
* Chemotherapy: Fatigue, hair loss, risk of infection.

## What is the chance that my prostate cancer will be cured with treatment?

Most prostate cancers detected early and confined to the prostate are highly curable. The chance of cure decreases if the cancer is high grade, high PSA, or has spread outside the prostate.

## If you had a friend or family member in my situation, what would you recommend?

Your doctor will base recommendations on your cancer’s risk category, overall health, and personal values, and will discuss the pros and cons of each option.

## Should I see a specialist? What will that cost, and will my insurance cover it?

You should see a urologist or oncologist specializing in prostate cancer. Costs and insurance coverage vary; your care team or insurance provider can help clarify what is covered and any out-of-pocket expenses.

## 

## **Diagnostic Considerations**

In most cases, the differential diagnoses of advanced prostate cancer do not present any difficulty. However, certain caveats must be considered.

Radiologic findings of bony metastases can mimic Paget disease of bone. Although bony metastases are blastic in nature, lytic lesions can occur, resulting in pathologic fractures. In men treated with luteinizing hormone–releasing hormone (LHRH), osteoporotic fractures must be distinguished from pathologic fractures.

Neurologic manifestations should be underscored. Sudden onset of weakness of the legs in an elderly man with a history of prostate cancer should raise the suspicion of spinal cord compression, necessitating emergency treatment (spinal cord decompression). Although brain metastases with associated neurologic manifestations are rare, they do occur with enough frequency to deserve recognition.

Lymphomas can manifest as pelvic masses and bone lesions. Although coexistence of lymphomas with prostate cancer has been reported, it is extremely rare.

Transitional cell carcinoma (TCC) and sarcoma of the prostate are more common in men who have undergone prior pelvic radiation therapy for prostate cancer than in men who have not. (The reported incidence of prostatic TCC ranges from 21.8% to 36.7%, depending mainly on the manner of examination.Over 90% of cases are associated with bladder cancer.) Likewise, squamous cell carcinoma of the prostate may be observed in men treated with hormone therapy. All of these can present as a large pelvic mass with or without metastases.

Small cell carcinoma of the prostate is rare, accounting for less than 1% of all prostate cancers. Pathologically, these tumors feature small cells with minimal cytoplasm, nuclear molding, fine chromatin pattern, extensive tumor necrosis/apoptosis, and a brisk mitotic rate. These cases may present as pure small cell carcinoma or mixed with a conventional prostatic adenocarcinoma. Other cases are initially diagnosed as prostatic adenocarcinoma and recur as small cell carcinoma after hormonal therapy. Clinically, small cell prostate cancer is characterized by extensive local disease; visceral disease; and low prostate-specific antigen (PSA) levels, even in patients with a large metastatic burden. Small cell carcinoma of the prostate is extremely aggressive, and the prognosis for these patients is dismal.

Prostatic stromal sarcomas are estimated to account for less than 0.1% of all prostate malignancies. Local invasion or aggressive spread, including metastasis in selected cases, is possible with these sarcomas but because of the rarity of these neoplasms, their true clinical behavior is not entirely known. The term stromal tumors of uncertain malignant potential (STUMP) describes a proliferation of stromal cells that is behaviorally and histologically distinct from benign hyperplasia and whose behavior cannot be predicted by its histologic appearance.

**The differential diagnosis for prostate cancer includes:**

* Acute bacterial prostatitis
* Prostatic abscess
* Chronic bacterial prostatitis
* Benign prostatic hyperplasia
* Nonbacterial prostatitis
* Tuberculosis of the genitourinary system

## **Epidemiology**

Internationally, the incidence of prostate cancer varies by more than 50-fold, with the highest rates being in North America, Australia, and northern and central Europe and the lowest rates being in southeastern and south-central Asia and northern Africa. [1, 17]

### Occurrence and mortality in the United States

In the United States, prostate cancer is the most common non cutaneous cancer in men. An estimated one in six White men and one in five Black men will be diagnosed with prostate cancer in their lifetime, with the likelihood increasing with age. The American Cancer Society estimates that 313,780 new cases of prostate cancer will be diagnosed in 2025. Prostate cancer is rarely diagnosed in men younger than 40 years, and it is uncommon in men younger than 50 years.

Between 1989 and 1992, incidence rates of prostate cancer increased dramatically in the United States, probably because of earlier diagnoses in asymptomatic men as a result of the increased use of serum PSA testing. In addition, the incidence of organ-confined disease at diagnosis increased because of PSA testing and standard digital rectal examination. After 1992, incidence rates declined markedly, decreasing from over 230 per 100,000 population to 97 per 100,000 population in 2014.Subsequently, however, rates began rising; the incidence increased by 3% annually from 2014 through 2019.

Advanced disease accounts for a growing percentage of new prostate cancer cases. A review of almost 800,000 cases of prostate cancer diagnosed from 2004–2013 found that although the incidence of low-risk prostate cancer decreased from 2007-2013 to 37% less than that of 2004, the annual incidence of metastatic prostate cancer during those years increased to 72% more than that of 2004. The increase in metastatic prostate cancer was greatest (92%) in men aged 55–69 years.In 2015–2019, incidence rates for regional and distant prostate cancer increased by 4-6% per year.

Prostate cancer mortality rates began to decline in the early 1990s, in all racial and ethnic populations, decreasing from 39.3 per 100,000 persons in 1991 to 18.6 per 100,000 in 2020.However, in 2015-2019, the decline in death rates slowed for Black and Hispanic men and ceased for White and Asian American/Pacific Islander men.The American Cancer Society estimates that 35,770 men will die of prostate cancer in 2025.

### Age-related demographics

Prostate cancer incidence increases as men age; as many as 60% of men over 65 years of age may be diagnosed with prostate cancer.Prostate cancer is most often diagnosed in men aged 65-74 years; median age at diagnosis is 66 years.

However, men as young as 17 years are experiencing an increasing incidence of prostate cancer in much of the world, including the United States, according to data from the Surveillance, Epidemiology, and End Results (SEER) program and the Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease (GBD) database. These younger patients frequently present with more advanced cancer and have worse survival than middle-aged and older men. Worldwide, the incidence of prostate cancer has increased in men ages 15 to 40 years at a steady rate averaging 2% per year since 1990. In the United States, this age group was more than 6 times more likely than older men to have distant disease at diagnosis.

### Racial demographics

In the United States, the incidence rate of prostate cancer is 70% higher in Black versus White men, and the prostate cancer mortality rate in Black men is 2-4 times higher than in every other racial and ethnic group.Worldwide, the incidence is highest in Blacks and Caribbean men of African descent, followed by Whites, Hispanics, and finally Asian men living in their native countries. Prostate cancer incidence is highest in countries with the highest socioeconomic index.

A cohort study of 7.8 million Veterans Affairs patients found that despite equal access to care in this setting, incidence rates of localized and advanced prostate cancer were nearly twice as high in Black (African American) veterans as in White ones. Of the veterans with localized prostate cancer, Blacks were younger than Whites (median age, 63 vs 65 years) and had higher prostate-specific antigen levels (> 20 ng/mL) at the time of diagnosis. However, outcomes were similar in patients who received the same treatment, with lowered risk of metastasis.

### Risk factors

Well-established risk factors for prostate include ethnicity, age, and country of residence. Additional risk factors include family history and genetic predisposition. For men with a family history (1 or more first-degree relatives) of breast cancer, the risk of prostate cancer diagnosis increases by 21%, and lethality increases by 34% compared with those without such history. Similarly, a family history of prostate cancer increases risk by 68% and lethality of disease by 72%, with a general trend favoring increases in risk according to earlier cancer onset in families.These associations have led to the identification of several germline mutations associated with hereditary prostate cancer, including *HOXB13,BRCA1, BRCA2,* DNA mismatch repair genes, *ATM, CHEK2, PALB2, NBN,* and *RAD51D.*

Discovery of these mutations has led to recommendations for the consideration of genetic testing for men with family histories that strongly suggest the presence of these mutations and men with metastatic castrate-resistant prostate cancer.In men referred for genetic testing, about 20% will have a known genetic variation while only 63% will have a significant family history that would guide genetic testing decision making.*BRCA1/2 and ATM* mutations have been found at significantly higher rates in men with lethal prostate cancer.Overall, genetic testing remains a novel and developing area of prostate cancer research, but it may ultimately inform screening, risk stratification, treatment aggressiveness, and (where currently applied) targeted systemic therapy for advanced disease.

An examination of cancer histories of 198 Lynch syndrome families, including probands and their first- through fourth-degree relatives, found that men with Lynch syndrome have a 2-fold higher risk of prostate cancer compared with the general population. Of the 4127 men involved in the study, 97 had prostate cancer. Median age at diagnosis was 65, with 11.5% diagnosed before age 50. The cumulative risk of prostate cancer for men with Lynch syndrome was 6.3% at age 60 and 30% at age 80, versus population-wide risk of 2.6% and 17.8%, respectively.

Several additional risk factors for prostate cancer are associated with either lower levels of evidence or conflicting evidence. Both increased body mass index (BMI) and additional components of the metabolic syndrome (eg, hyperinsulinemia, waist circumference) have been variably associated with both increased prostate cancer incidence and possibly increased recurrence after definitive therapy.

Increasing evidence suggests that the gut and genitourinary microbiome play a role in prostate cancer.Banerjee et al found that the microbiome signature (viral, bacterial, fungal, and parasitic elements) in prostate cancer samples differed from the microbiome signature in benign prostate hyperplasia controls. These authors also identified three distinct prostate cancer–specific microbiome signatures that correlated with different cancer grades, stages, and scores.

Hurst et al identified bacteria in urine collected after digital rectal examination and in secretions from prostatectomy samples and reported an association between the presence of bacteria and prostate cancer risk; the percentage of urine samples positive for bacteria rose from 17% in patients with low-risk prostate cancer to 100% of those with high-risk disease. In addition, the presence of five specific anaerobic genera, including three novel bacteria, was associated with aggressive prostate cancer risk.

Tobacco smoking, nutritional supplementation and/or deficiency, activity, and dietary components have also demonstrated variable association with prostate cancer incidence and/or mortality.Supplements with selenium and vitamin E were prospectively evaluated for the prevention of prostate cancer in the SELECT trial, which demonstrated an increase in prostate cancer cases for those given vitamin E only and no effect of selenium supplementation.The effect observed for vitamin E was not seen in other studies.The significant heterogeneity surrounding these risk factors suggests that further, nuanced evaluation is required before they can be classified as risk factors for prostate cancer or prostate cancer severity.

## **Prostate Cancer Genomic Data**

## Key Genomic Alterations and Their Clinical Implications

* BRCA1/2 Mutations:  
  BRCA2 mutations, in particular, are associated with aggressive prostate cancer and poorer progression-free survival (PFS) and overall survival (OS). These mutations also help identify patients who may benefit from PARP inhibitors and other targeted therapies.
* TP53, RB1, and PTEN:  
  Mutations in TP53, RB1, and PTEN are linked to significantly shorter PFS and worse OS in metastatic hormone-sensitive prostate cancer (mHSPC), indicating a poorer prognosis and higher risk of treatment resistance.
* Chromosomal Instability Signatures:  
  Genomic tests that assess chromosomal instability can predict resistance to taxane-based chemotherapy in metastatic prostate cancer, allowing for more personalized treatment selection.
* Circulating Tumor DNA (ctDNA):  
  ctDNA analysis is emerging as a real-time tool to monitor tumor evolution, detect resistance mechanisms, and guide therapy adjustments, especially in patients with high-risk mutations like BRCA2.
* RNA and Multiplex Genomic Signatures:  
  Tests like Decipher and Prolaris analyze gene expression profiles or cell-cycle progression genes from prostate tissue to stratify risk of recurrence, metastasis, and cancer-specific mortality. These scores are used to refine decisions about adjuvant therapy, active surveillance, and overall prognosis.
* Emerging Biomarkers and AI Analysis:  
  Biomarker-driven approaches, including AI-driven analysis of genomic data, are being used to better identify high-risk patients and optimize use of therapies such as abiraterone or PARP inhibitors

## **Prostate Cancer Doctor-Patient Conversation**

Doctor:  
"Thank you for coming in today. I have reviewed your biopsy results, and they show that you have prostate cancer. I know this is a lot to take in, and I want you to know that we are here to support you through every step."

Patient:  
"I was worried about this. What does this mean for me now?"

Doctor:  
"Your cancer is localized to the prostate and is considered low to intermediate risk, based on your PSA level and the Gleason score from your biopsy. This gives us several good treatment options, and the outlook is generally favorable."

Patient:  
"What are my treatment options?"

Doctor:  
"We can consider active surveillance, which means closely monitoring the cancer with regular check-ups and only treating if it shows signs of growing. Other options include surgery to remove the prostate or radiation therapy. Each treatment has potential side effects, such as changes in urinary or sexual function, and we can talk through these in detail."

Patient:  
"How do I decide what’s best for me?"

Doctor:  
"It’s important to consider your personal preferences, lifestyle, and any other health conditions you have. Some men prefer to avoid immediate treatment and its side effects, while others feel more comfortable taking action right away. I’ll provide you with information about each option, and we can involve other specialists, like a radiation oncologist or a surgeon, if you’d like."

Patient:  
"Are there any tests or follow-up I need right now?"

Doctor:  
"We’ll repeat your PSA test in a few weeks and may do an MRI to get more detailed images of your prostate. If you choose active surveillance, you’ll have regular PSA tests and occasional biopsies. If you choose surgery or radiation, we’ll schedule those procedures and provide detailed instructions."

Patient:  
"Is there support available if I have more questions or need help coping?"

Doctor:  
"Absolutely. We have a nurse navigator and support groups for men with prostate cancer. I’ll also give you written information to take home. Please feel free to call or email me with any questions that come up."

Patient:  
"Thank you for explaining everything."

Doctor:  
"You’re welcome. Take your time to think about your options, and let’s schedule a follow-up appointment so we can discuss your decision and next steps. We’re here for you."

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**BLADDER CANCER**

**DEFINITION AND DESCRIPTION**

Bladder cancer is a common type of cancer that begins in the cells of the bladder. The bladder is a hollow muscular organ in your lower abdomen that stores urine.

Bladder cancer most often begins in the cells (urothelial cells) that line the inside of your bladder. Urothelial cells are also found in your kidneys and the tubes (ureters) that connect the kidneys to the bladder. Urothelial cancer can happen in the kidneys and ureters, too, but it's much more common in the bladder.

Most bladder cancers are diagnosed at an early stage, when the cancer is highly treatable. But even early-stage bladder cancers can come back after successful treatment. For this reason, people with bladder cancer typically need follow-up tests for years after treatment to look for bladder cancer that recurs.

**CAUSES**

Bladder cancer begins when cells in the bladder develop changes (mutations) in their DNA. A cell's DNA contains instructions that tell the cell what to do. The changes tell the cell to multiply rapidly and to go on living when healthy cells would die. The abnormal cells form a tumor that can invade and destroy normal body tissue. In time, the abnormal cells can break away and spread (metastasize) through the body.

### **Types of bladder cancer**

Different types of cells in your bladder can become cancerous. The type of bladder cell where cancer begins determines the type of bladder cancer. Doctors use this information to determine which treatments may work best for you.

Types of bladder cancer include:

* **Urothelial carcinoma.** Urothelial carcinoma, previously called transitional cell carcinoma, occurs in the cells that line the inside of the bladder. Urothelial cells expand when your bladder is full and contract when your bladder is empty. These same cells line the inside of the ureters and the urethra, and cancers can form in those places as well. Urothelial carcinoma is the most common type of bladder cancer in the United States.
* **Squamous cell carcinoma.** Squamous cell carcinoma is associated with chronic irritation of the bladder — for instance, from an infection or from long-term use of a urinary catheter. Squamous cell bladder cancer is rare in the United States. It's more common in parts of the world where a certain parasitic infection (schistosomiasis) is a common cause of bladder infections.
* **Adenocarcinoma.** Adenocarcinoma begins in cells that make up mucus-secreting glands in the bladder. Adenocarcinoma of the bladder is very rare.

Some bladder cancers include more than one type of cell.

**Risk factors**

Factors that may increase bladder cancer risk include:

* **Smoking.** Smoking cigarettes, cigars or pipes may increase the risk of bladder cancer by causing harmful chemicals to accumulate in the urine. When you smoke, your body processes the chemicals in the smoke and excretes some of them in your urine. These harmful chemicals may damage the lining of your bladder, which can increase your risk of cancer.
* **Increasing age.** Bladder cancer risk increases as you age. Though it can occur at any age, most people diagnosed with bladder cancer are older than 55.
* **Being male.** Men are more likely to develop bladder cancer than women are.
* **Exposure to certain chemicals.** Your kidneys play a key role in filtering harmful chemicals from your bloodstream and moving them into your bladder. Because of this, it's thought that being around certain chemicals may increase the risk of bladder cancer. Chemicals linked to bladder cancer risk include arsenic and chemicals used in the manufacture of dyes, rubber, leather, textiles and paint products.
* **Previous cancer treatment.** Treatment with the anti-cancer drug cyclophosphamide increases the risk of bladder cancer. People who received radiation treatments aimed at the pelvis for a previous cancer have a higher risk of developing bladder cancer.
* **Chronic bladder inflammation.** Chronic or repeated urinary infections or inflammations (cystitis), such as might happen with long-term use of a urinary catheter, may increase the risk of a squamous cell bladder cancer. In some areas of the world, squamous cell carcinoma is linked to chronic bladder inflammation caused by the parasitic infection known as schistosomiasis.
* **Personal or family history of cancer.** If you've had bladder cancer, you're more likely to get it again. If one of your blood relatives — a parent, sibling or child — has a history of bladder cancer, you may have an increased risk of the disease, although it's rare for bladder cancer to run in families. A family history of Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), can increase the risk of cancer in the urinary system, as well as in the colon, uterus, ovaries and other organs.

**Symptoms**

Bladder cancer signs and symptoms may include:

* Blood in urine (hematuria), which may cause urine to appear bright red or cola colored, though sometimes the urine appears normal and blood is detected on a lab test
* Frequent urination
* Painful urination
* Back pain

### 

### **When to see a doctor**

If you notice that you have discolored urine and are concerned it may contain blood, make an appointment with your doctor to get it checked. Also make an appointment with your doctor if you have other signs or symptoms that worry you.

**DIAGNOSIS**

Tests and procedures used to diagnose bladder cancer may include:

* **Using a scope to examine the inside of your bladder (cystoscopy).** To perform cystoscopy, your doctor inserts a small, narrow tube (cystoscope) through your urethra. The cystoscope has a lens that allows your doctor to see the inside of your urethra and bladder, to examine these structures for signs of disease. Cystoscopy can be done in a doctor's office or in the hospital.
* **Removing a sample of tissue for testing (biopsy).** During cystoscopy, your doctor may pass a special tool through the scope and into your bladder to collect a cell sample (biopsy) for testing. This procedure is sometimes called transurethral resection of bladder tumor (TURBT). TURBT can also be used to treat bladder cancer.
* **Examining a urine sample (urine cytology).** A sample of your urine is analyzed under a microscope to check for cancer cells in a procedure called urine cytology.
* **Imaging tests.** Imaging tests, such as computerized tomography (CT) urogram or retrograde pyelogram, allow your doctor to examine the structures of your urinary tract.  
  During a CT urogram, a contrast dye injected into a vein in your hand eventually flows into your kidneys, ureters and bladder. X-ray images taken during the test provide a detailed view of your urinary tract and help your doctor identify any areas that might be cancer.  
  Retrograde pyelogram is an X-ray exam used to get a detailed look at the upper urinary tract. During this test, your doctor threads a thin tube (catheter) through your urethra and into your bladder to inject contrast dye into your ureters. The dye then flows into your kidneys while X-ray images are captured.

### **Determining the extent of the cancer**

After confirming that you have bladder cancer, your doctor may recommend additional tests to determine whether your cancer has spread to your lymph nodes or to other areas of your body.

Tests may include:

* CT scan
* Magnetic resonance imaging (MRI)
* Positron emission tomography (PET)
* Bone scan
* Chest X-ray

Your doctor uses information from these procedures to assign your cancer a stage. The stages of bladder cancer are indicated by Roman numerals ranging from 0 to IV. The lowest stages indicate a cancer that's confined to the inner layers of the bladder and that hasn't grown to affect the muscular bladder wall. The highest stage — stage IV — indicates cancer that has spread to lymph nodes or organs in distant areas of the body

### **Bladder cancer grade**

Bladder cancers are further classified based on how the cancer cells appear when viewed through a microscope. This is known as the grade, and your doctor may describe bladder cancer as either low grade or high grade:

* **Low-grade bladder cancer.** This type of cancer has cells that are closer in appearance and organization to normal cells (well differentiated). A low-grade tumor usually grows more slowly and is less likely to invade the muscular wall of the bladder than is a high-grade tumor.
* **High-grade bladder cancer.** This type of cancer has cells that are abnormal-looking and that lack any resemblance to normal-appearing tissues (poorly differentiated). A high-grade tumor tends to grow more aggressively than a low-grade tumor and may be more likely to spread to the muscular wall of the bladder and other tissues and organs.

**Treatment**

Treatment options for bladder cancer depend on a number of factors, including the type of cancer, grade of the cancer and stage of the cancer, which are taken into consideration along with your overall health and your treatment preferences.

Bladder cancer treatment may include:

* **Surgery,** to remove the cancer cells
* **Chemotherapy in the bladder (intravesical chemotherapy),** to treat cancers that are confined to the lining of the bladder but have a high risk of recurrence or progression to a higher stage
* **Chemotherapy for the whole body (systemic chemotherapy),** to increase the chance for a cure in a person having surgery to remove the bladder, or as a primary treatment when surgery isn't an option
* **Radiation therapy,** to destroy cancer cells, often as a primary treatment when surgery isn't an option or isn't desired
* **Immunotherapy,** to trigger the body's immune system to fight cancer cells, either in the bladder or throughout the body
* **Targeted therapy,** to treat advanced cancer when other treatments haven't helped

A combination of treatment approaches may be recommended by your doctor and members of your care team.

### **Bladder cancer surgery**

Approaches to bladder cancer surgery might include:

* **Transurethral resection of bladder tumor (TURBT).** TURBT is a procedure to diagnose bladder cancer and to remove cancers confined to the inner layers of the bladder — those that aren't yet muscle-invasive cancers. During the procedure, a surgeon passes an electric wire loop through a cystoscope and into the bladder. The electric current in the wire is used to cut away or burn away the cancer. Alternatively, a high-energy laser may be used.  
  Because doctors perform the procedure through the urethra, you won't have any cuts (incisions) in your abdomen.  
  As part of the TURBT procedure, your doctor may recommend a one-time injection of cancer-killing medication (chemotherapy) into your bladder to destroy any remaining cancer cells and to prevent cancer from coming back. The medication remains in your bladder for a period of time and then is drained.
* **Cystectomy.** Cystectomy is surgery to remove all or part of the bladder. During a partial cystectomy, your surgeon removes only the portion of the bladder that contains a single cancerous tumor.  
  A radical cystectomy is an operation to remove the entire bladder and the surrounding lymph nodes. In men, radical cystectomy typically includes removal of the prostate and seminal vesicles. In women, radical cystectomy may involve removal of the uterus, ovaries and part of the vagina.  
  Radical cystectomy can be performed through an incision on the lower portion of the belly or with multiple small incisions using robotic surgery. During robotic surgery, the surgeon sits at a nearby console and uses hand controls to precisely move robotic surgical instruments.
* **Neobladder reconstruction.** After a radical cystectomy, your surgeon must create a new way for urine to leave your body (urinary diversion). One option for urinary diversion is neobladder reconstruction. Your surgeon creates a sphere-shaped reservoir out of a piece of your intestine. This reservoir, often called a neobladder, sits inside your body and is attached to your urethra. The neobladder allows most people to urinate normally. A small number of people difficulty emptying the neobladder and may need to use a catheter periodically to drain all the urine from the neobladder.
* **Ileal conduit.** For this type of urinary diversion, your surgeon creates a tube (ileal conduit) using a piece of your intestine. The tube runs from your ureters, which drain your kidneys, to the outside of your body, where urine empties into a pouch (urostomy bag) you wear on your abdomen.
* **Continent urinary reservoir.** During this type of urinary diversion procedure, your surgeon uses a section of intestine to create a small pouch (reservoir) to hold urine, located inside your body. You drain urine from the reservoir through an opening in your abdomen using a catheter a few times each day.

### **Chemotherapy**

Chemotherapy uses drugs to kill cancer cells. Chemotherapy treatment for bladder cancer usually involves two or more chemotherapy drugs used in combination.

Chemotherapy drugs can be given:

* **Through a vein (intravenously).** Intravenous chemotherapy is frequently used before bladder removal surgery to increase the chances of curing the cancer. Chemotherapy may also be used to kill cancer cells that might remain after surgery. In certain situations, chemotherapy may be combined with radiation therapy.
* **Directly into the bladder (intravesical therapy).** During intravesical chemotherapy, a tube is passed through your urethra directly to your bladder. The chemotherapy is placed in the bladder for a set period of time before being drained. It can be used as the primary treatment for superficial bladder cancer, where the cancer cells affect only the lining of the bladder and not the deeper muscle tissue.

### **Radiation therapy**

Radiation therapy uses beams of powerful energy, such as X-rays and protons, to destroy the cancer cells. Radiation therapy for bladder cancer usually is delivered from a machine that moves around your body, directing the energy beams to precise points.

Radiation therapy is sometimes combined with chemotherapy to treat bladder cancer in certain situations, such as when surgery isn't an option or isn't desired.

### **Immunotherapy**

Immunotherapy is a drug treatment that helps your immune system to fight cancer.

Immunotherapy can be given:

* **Directly into the bladder (intravesical therapy).** Intravesical immunotherapy might be recommended after TURBT for small bladder cancers that haven't grown into the deeper muscle layers of the bladder. This treatment uses bacillus Calmette-Guerin (BCG), which was developed as a vaccine used to protect against tuberculosis. BCG causes an immune system reaction that directs germ-fighting cells to the bladder.
* **Through a vein (intravenously).** Immunotherapy can be given intravenously for bladder cancer that's advanced or that comes back after initial treatment. Several immunotherapy drugs are available. These drugs help your immune system identify and fight the cancer cells.

### **Targeted therapy**

Targeted therapy drugs focus on specific weaknesses present within cancer cells. By targeting these weaknesses, targeted drug treatments can cause cancer cells to die. Your cancer cells may be tested to see if targeted therapy is likely to be effective.

Targeted therapy may be an option for treating advanced bladder cancer when other treatments haven't helped.

### **Bladder preservation**

In certain situations, people with muscle-invasive bladder cancer who don't want to undergo surgery to remove the bladder may consider trying a combination of treatments instead. Known as trimodality therapy, this approach combines TURBT, chemotherapy and radiation therapy.

First, your surgeon performs a TURBT procedure to remove as much of the cancer as possible from your bladder while preserving bladder function. After TURBT, you undergo a regimen of chemotherapy along with radiation therapy.

If, after trying trimodality therapy, not all of the cancer is gone or you have a recurrence of muscle-invasive cancer, your doctor may recommend a radical cystectomy.

### **After bladder cancer treatment**

Bladder cancer may recur, even after successful treatment. Because of this, people with bladder cancer need follow-up testing for years after successful treatment. What tests you'll have and how often depends on your type of bladder cancer and how it was treated, among other factors.

In general, doctors recommend a test to examine the inside of your urethra and bladder (cystoscopy) every three to six months for the first few years after bladder cancer treatment. After a few years of surveillance without detecting cancer recurrence, you may need a cystoscopy exam only once a year. Your doctor may recommend other tests at regular intervals as well.

People with aggressive cancers may undergo more-frequent testing. Those with less aggressive cancers may undergo testing less often.

**Prevention**

Although there's no guaranteed way to prevent bladder cancer, you can take steps to help reduce your risk. For instance:

* **Don't smoke.** If you don't smoke, don't start. If you smoke, talk to your doctor about a plan to help you stop. Support groups, medications and other methods may help you quit.
* **Take caution around chemicals.** If you work with chemicals, follow all safety instructions to avoid exposure.
* **Choose a variety of fruits and vegetables.** Choose a diet rich in a variety of colorful fruits and vegetables. The antioxidants in fruits and vegetables may help reduce your risk of cancer.

## **Diagnostic Considerations**

The presentation in bladder cancer may resemble a urinary tract infection (UTI), or the two conditions may coexist. Both UTIs and bladder cancer can cause hematuria, and bacteriuria occurs in about 50% of patients with squamous cell carcinoma (SCC). Patients with bladder cancer may have spontaneous resolution of gross or microscopic hematuria, which may lull the patient and the clinician into erroneously believing that no significant entity is present. UTIs are usually associated with irritative voiding symptoms (eg, dysuria, frequency, urgency). However, patients who have carcinoma in situ (CIS) may also present with irritative voiding symptoms.

CIS is often misdiagnosed as a bladder infection and treated as such. Patients with irritative voiding symptoms that do not resolve with treatment for UTI require further evaluation. The investigation should include urine cultures for fungi and tuberculosis, as well as cytology studies.

The first step in a bladder cancer workup involves the patient undergoing cystoscopy in an office setting. Cystoscopy in patients with CIS may reveal a characteristic red, velvety appearance that resembles an area of inflammation. In some cases, however, CIS is not visible on gross inspection. If there is a suspicious area or visible tumor, a biopsy or resection should be done during repeat cystoscopy performed in the operating room.

Diagnostic tests include a urine cytology test and/or tests for one of several available bladder cancer markers. These tests are highly sensitive in detecting CIS. Bladder biopsies are needed to firmly establish a diagnosis. Urinary cytology is highly specific for urothelial bladder cancer, with improved sensitivity for high-grade tumors and cytology obtained by bladder wash or barbotage.

Unfortunately, urinary cytology is not especially helpful in early diagnosis of SCCs. Most of these tumors are not diagnosed until they are at an advanced stage.

With small cell carcinoma, the main differential diagnoses are high-grade urothelial carcinoma, lymphoma, and sarcoma. Additionally, metastatic small cell carcinoma should be ruled out based on the available clinical information. Because small cell carcinoma of the urinary bladder is often mixed with urothelial carcinoma and because any presence of small cell carcinoma is justifiable to render the diagnosis, it is important to thoroughly examine the tumor tissue.

Benign bladder lesions include the following:

* Inflammatory myofibroblastic tumor is a spindled soft tissue lesion that is often mistaken for sarcoma; most cases follow an indolent and often benign clinical course, and respond well to surgical resection only; however, follow-up for local recurrence is indicated
* Squamous papilloma is composed of papillary cores with overlying histologically benign squamous epithelium; most cases have been in women in the fourth to seventh decade of life; it typically has an excellent prognosis with total excision, but follow-up is indicated, as recurrences have in up to one third of cases
* Inverted papilloma is a rare, benign endophytic urothelial tumor that grossly is a pedunculated polypoid lesion or a sessile lesion with a smooth surface, covered with normal-appearing urothelial epithelium, and are usually located in the trigone; inverted papillomas are of moderate significance due to their variable similarity to inverted urothelial carcinoma, which holds a much more aggressive prognosis; histologic distinction of the two entities can sometimes be difficult, in which case immunohistochemistry can be of assistance

## **Differential Diagnoses**

* Urinary Tract Infection (UTI) and Cystitis (Bladder Infection) in Females
* Hemorrhagic Cystitis
* Nephrolithiasis
* Renal Cell Carcinoma
* Renal Transitional Cell Carcinoma
* Urinary Tract Infection (UTI) in Males

## 

## **Epidemiology**

### Occurrence in the United States

The American Cancer Society estimates that 84,870 new cases of bladder cancer will be diagnosed in the United States in 2025 and that 17,420 people will die of the disease.The incidence of bladder cancer increases with age, with the median age at diagnosis being 73 years; bladder cancer is rarely diagnosed before age 40 years.

Bladder cancer is about 4 times more common in men than in women.The male predominance in bladder cancer in the United States reflects the prevalence of urothelial carcinoma (transitional cell carcinoma). With small cell carcinoma—in contrast to urothelial carcinoma—the male-to-female incidence ratio is 1:2.

Bladder cancer is the fourth most common cancer in men in the United States, after prostate, lung, and colorectal cancer, but it is not among the top 10 cancers in women. Accordingly, more men than women are expected to die of bladder cancer in 2025, with 12,640 deaths in men versus 4780 in women.Nevertheless, women generally have a worse prognosis than men.

The incidence of bladder cancer is twice as high in White men as in Black men in the United States. However, Blacks have a worse prognosis than Whites.

From 2000 to 2019, incidence and death rates for bladder cancer decreased in most racial and ethnic groups in both men and women in the US. On average, incidence rates decreased by 1.88% annually in men and 1.34% in women; death rates decreased by 2.16% in men and 2.44% in women. However, incidence rates showed a steady increase in American Indian and Alaska Native men and women, and death rates stabilized in Asian American and Pacific Islander men and Hispanic women.

Limited data indicate that small cell carcinoma of the urinary bladder probably has the same epidemiologic characteristics as urothelial carcinoma. Patients are more likely to be male and older than 50 years.

### International occurrence

Worldwide, bladder cancer is diagnosed in approximately 275,000 people each year, and about 108,000 die of this disease. In industrialized countries, 90% of bladder cancers are urothelial carcinomas. In developing countries—particularly in the Middle East and Africa—the majority of bladder cancers are SCCs, and most of these cancers are secondary to *Schistosoma haematobium* infection. Urothelial carcinoma is reported to be the most common urologic cancer in China.

In Africa, the highest incidence of SCC has been seen in schistosomal-endemic areas, notably Sudan and Egypt, where SCC ranges from two thirds to three quarters of all malignant tumors of the bladder. Since the turn of the century, a few studies from Egypt have shown a reversal of this trend due to the better control of schistosomiasis in the region, whereas in other parts of Africa the association is unchanged.Increased smoking incidence is believed to have contributed to the shift in Egypt toward urothelial carcinoma, which has a stronger smoking association.

## **Outlook / Prognosis**

Left untreated, bladder cancer may spread to other parts of your body. Cancer that’s metastasized, or spread, may affect how long you’ll live with bladder cancer. Like many types of cancer, early detection and treatment increase the chance of living longer with bladder cancer. According to the National Cancer Institute, 96% of people who received treatment for early-stage cancer were alive five years after diagnosis. Overall, 77% of people with bladder cancer were alive five years after diagnosis.

## **Living With**

About half of all people with bladder cancer have early-stage cancer that’s relatively easy to treat. But bladder cancer often comes back (recurs). People who’ve had bladder cancer will need regular checkups after treatment. Being vigilant about follow-up care is one thing you can do to take care of yourself. Some other suggestions from the Bladder Cancer Advocacy Network include:

* Follow a heart-healthy diet: Plan menus that include skinless poultry and fish, low-fat dairy products, nuts and legumes, and a variety of fruits and vegetables.
* Focus on high-fiber foods: Bladder cancer treatment may cause digestive issues and a fiber-rich diet may help.
* Get some exercise: Gentle exercise may help manage stress.
* Connect with others: Bladder cancer often comes back. It’s not easy to have a rare disease that’s likely to return. Connecting with people who understand what you’re going through may help.

#### **Urinary diversion**

Some people with bladder cancer need surgery that removes their bladder — and their bodies’ natural reservoir for pee. There are three types of urinary diversion surgeries. All three types involve surgically converting part of your intestine to become a passage tube for pee or a reservoir for storing pee.

Urinary diversion may be a challenging lifestyle change. If you’ll need urinary diversion surgery, ask your healthcare provider to explain each surgery type’s advantages and disadvantages. That way, you’ll know what to expect and how to take care of yourself.

**QUESTION AND ANSWER SET**

What stage of bladder cancer do I have?  
Your stage depends on how deeply the cancer has invaded the bladder wall and whether it has spread to lymph nodes or other organs. Staging is determined by imaging, cystoscopy, and sometimes surgery. Ask your doctor for your specific stage, as this guides treatment choices.

What are possible treatments?

* Non–muscle-invasive bladder cancer (NMIBC): Transurethral resection (TURBT), followed by intravesical therapy (BCG or chemotherapy like mitomycin). Newer options include gene and immunotherapies, and novel drug delivery systems.
* Muscle-invasive bladder cancer (MIBC): May require radical cystectomy (bladder removal) with or without chemotherapy, or bladder-sparing approaches using chemotherapy and radiation. Immunotherapy and targeted agents are increasingly used.
* Metastatic disease: Combination chemotherapy, immunotherapy (e.g., pembrolizumab, nivolumab), and targeted therapies. Clinical trials offer access to cutting-edge options.

What are treatment side effects?

* Surgery: Pain, infection risk, changes in urinary function, and possible need for urinary diversion.
* Intravesical therapy: Bladder irritation, urgency, and mild flu-like symptoms.
* Chemotherapy: Nausea, fatigue, hair loss, infection risk.
* Immunotherapy: Fatigue, skin rash, diarrhea, rare immune-related complications.
* Radiation: Urinary and bowel irritation, fatigue.

Will I need surgery?  
Surgery (TURBT) is standard for NMIBC. Radical cystectomy is often recommended for muscle-invasive or high-risk disease, but bladder-sparing options may be available, especially with new therapies and clinical trials.

How will surgery affect my daily life?  
After cystectomy, you may need a urinary diversion (like an ileal conduit or neobladder). This can affect urination, physical activity, and body image. Many patients adapt well with support and education, but lifestyle changes are common.

How often does bladder cancer come back?  
Bladder cancer, especially NMIBC, has a high recurrence rate—up to 50–70% for some patients. Regular surveillance with cystoscopy and urine tests is required.

How do you treat recurrent bladder cancer?  
Options depend on prior treatments and cancer stage. They may include repeat TURBT, additional intravesical therapy, radical cystectomy, or systemic treatments like immunotherapy or chemotherapy. Clinical trials are often considered for recurrent cases.

Are there any cutting-edge clinical trials available?  
Yes. Trials are evaluating gene therapy, novel immunotherapies, targeted agents, and new drug combinations. Ask your doctor about eligibility for current studies, as these can provide access to the latest treatments.

Do I have bladder cancer or could my symptoms be caused by another condition?  
Symptoms like blood in urine or urinary changes can also result from infections, stones, or prostate issues. Diagnosis is confirmed by cystoscopy, biopsy, and imaging.

Will I need any additional tests?  
You may need repeat cystoscopies, imaging (CT, MRI), urine cytology, or molecular testing to confirm diagnosis, stage the cancer, and plan treatment.

Can any treatments cure my bladder cancer?  
Yes—especially if detected early and confined to the bladder lining. Cure rates are high for NMIBC (over 90% 5-year survival). Muscle-invasive cancer is also potentially curable, especially with surgery and/or chemotherapy. Advanced disease is harder to cure, but long-term remission is possible with new therapies.

What are the potential risks of each treatment?  
Risks depend on the specific treatment but may include infection, bleeding, organ damage, urinary or sexual dysfunction, and side effects from chemo or immunotherapy. Your doctor will explain risks and how they apply to you.

Is there one treatment that you feel is best for me?  
The best treatment depends on your cancer’s stage, grade, overall health, and preferences. Your care team will recommend options tailored to your situation and discuss the pros and cons of each.

Should I see a specialist? What will that cost, and will my insurance cover it?  
Seeing a urologist or oncologist specializing in bladder cancer is highly recommended. Most insurance plans cover specialist care, but check with your provider for details on coverage and costs.

Is there a generic alternative to the medicine you're prescribing me?  
Many chemotherapy and supportive medications have generic versions. Ask your doctor or pharmacist if a generic is available for your prescribed treatment.

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## **Urine Tumor Markers**

More than 30 urinary biomarkers have been reported for use in bladder cancer diagnosis, but only a few are commercially available; the remainder are still being tested.In addition to urine cytology, tests approved or cleared for marketing by the US Food and Drug Administration (FDA) for bladder cancer diagnosis and/or surveillance include the following:

* BTA *stat*: Bladder tumor antigen point of care immunoassay
* BTA TRAK: Reference laboratory immunoassay
* Cxbladder: Measures the expression of 5 genes (*MDK, HOXA13,CDC2, IGFBP5, CXCR2*)
* NMP22 BladderChek: Nuclear matrix protein–22 point of care qualitative immunoassay
* NMP22 Bladder Cancer Test: In vitro quantitative enzyme-linked immunosorbent assay (ELISA)
* uCyt+ (formerly ImmunoCyt): Fluorescent monoclonal antibodies against M344, LDQ10, and 19A211
* Vysis UroVysion: Fluorescence in situ hybridization (FISH) probe set
* Xpert Bladder Cancer Monitor: Measures mRNA (ABL1, CRH, IGF2, UPK1B,ANXA10) in voided urine by reverse transcription–polymerase chain reaction (RT-PCR).

For the present, cystoscopy remains the gold standard for detecting bladder cancers. However, it is invasive, relatively expensive, and operator dependent, and has potential complications that include infection, bleeding, perforation, and urinary retention.

Urine cytology is still the most accurate noninvasive test for bladder cancer that is in routine clinical use, with a sensitivity of 80–90% and a specificity of 98–100% for detection of high-grade lesions and carcinoma in situ (CIS). The disadvantages of urine cytology are that it is relatively ineffective at detecting low-grade malignancy, and benign inflammatory conditions may result in false positive results

## **Medication Summary**

The combination of methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin (MVAC) is the standard treatment for metastatic bladder cancer. No proven role exists for adjuvant chemotherapy. MVAC has substantial toxicity, which must be weighed against the expected benefit. The major dose-limiting toxicity is myelosuppression.

Newer combination regimens show response rates and median survival comparable to those for MVAC but with less toxicity. Gemcitabine plus cisplatin is now considered a first-line treatment for bladder cancer. Therapy with programmed cell death ligand 1 (PD-L1) inhibitors (eg, atezolizumab, nivolumab, durvalumab, avelumab, pembrolizumab) is now approved by the US Food and Drug Administration (FDA) for advanced urothelial carcinoma.

Erdafitinib is the first fibroblast growth factor receptor (FGFR) inhibitor approved by the FDA for urothelial carcinoma, in April 2019. The first anti-nectin-4 monoclonal antibody, enfortumab vedotin, was approved for urothelial carcinoma in December 2019. The first gene therapy, nadofaragene firadenovec, was approved in 2022. Nogapendekin alfa inbakicept, an interleukin-15 agonist, was approved in 2024. It is indicated in combination with BCG for treatment of adults with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.

## **Antineoplastics, Antimetabolite**

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These agents inhibit cell growth and proliferation. They interfere with DNA synthesis by blocking the methylation of deoxyuridylic acid.

## Fluorouracil (Adrucil)

Fluorouracil is a pyrimidine antimetabolite. Several mechanisms of action have been proposed, including inhibition of thymidylate synthase and inhibition of RNA synthesis. This agent is also a potent radiosensitizer. Although not approved by the FDA for this indication, fluorouracil is often used as a treatment for bladder cancer, commonly in combination with cisplatin.

## Methotrexate (Trexall, Rasuvo, Otrexup, Xatmep)

Methotrexate inhibits dihydrofolate reductase (DHFR), causing a block in the reduction of dihydrofolate to tetrahydrofolate. This inhibits the formation of thymidylate and purines and arrests DNA, RNA, and protein synthesis.Common toxicities include mucositis and myelosuppression. It is often used as a treatment for bladder cancer, although that is not an FDA-approved indication.

## Gemcitabine (Gemzar)

Gemcitabine is a pyrimidine analog. After intracellular metabolism to its active nucleotide, it inhibits ribonucleotide reductase and competes with deoxycytidine triphosphate for incorporation into DNA. Although it does not have FDA approval for this indication, it is often used as a treatment for bladder cancer. Gemcitabine is used in combination with cisplatin for the treatment of advanced or metastatic bladder cancer. It is also used as an intraveiscal treatment.

## Pemetrexed (Alimta)

Pemetrexed disrupts the folate-dependant metabolic processes important for cell replication, inhibits the enzymes involved in folate metabolism and DNA synthesis, and inhibits protein synthesis. Although it does not have FDA approval for this indication, it is often used for the treatment of metastatic bladder cancer. Folic acid and vitamin B12 are typically given prior to initiation of treatment. Dexamethasone is also given with pemetrexed, to minimize cutaneous reactions.

## **Antineoplastics, Vinca Alkaloid**

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Vinca alkaloids act on the M and S phases of mitosis, inhibiting microtubule formation and inhibiting DNA/RNA synthesis.

## Vinblastine

A vinca alkaloid with a cytotoxic effect (as a result of causing mitotic arrest), vinblastine binds to a specific site on tubulin, prevents polymerization of tubulin dimers, and inhibits microtubule formation. Although not FDA approved for this indication, vinblastine is often used as a treatment for bladder cancer in combination with a chemotherapy regimen.

Vinblastine is approved for intravenous use only; the FDA has issued a black box warning regarding possible death with intrathecal administration. Vinblastine is a moderate vesicant and extravasation should be avoided.

## **Antineoplastics, Anthracycline**

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Anthracycline antineoplastics inhibit DNA and RNA synthesis by steric obstruction. They intercalate between DNA base pairs and trigger DNA cleavage by topoisomerase II.

## Doxorubicin (Adriamycin)

Doxorubicin is an anthracycline antineoplastic that causes DNA strand breakage through effects on topoisomerase II and direct intercalation into DNA, which causes DNA polymerase inhibition. It has a labeled indication for the treatment of bladder cancer. The largest benefit this agent has compared with other intravesical chemotherapeutic agents is its low cost and ability to decrease tumor recurrence.This drug has several black box warnings, including bone marrow suppression, myocardial toxicity, and secondary malignancy.

## Valrubicin (Valstar)

Valrubicin is a semisynthetic analog of doxorubicin that inhibits incorporation of nucleosides into nucleic acids. It is indicated for intra vesicular treatment of bladder carcinoma in situ (CIS) that is refractory to treatment with bacillus Calmette-Guérin (BCG).

## **Antineoplastics, Alkylating**

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These agents inhibit cell growth and proliferation. They inhibit DNA synthesis by the formation of DNA cross-links. Alkylating agents can have serious adverse effects, including bone marrow suppression, anaphylactic-like reactions, ototoxicity, renal toxicity, and vomiting.

## Cisplatin

Cisplatin is a platinum-containing compound that exerts an antineoplastic effect by covalently binding to DNA, with preferential binding to the N-7 position of guanine and adenosine. It can react with 2 different sites on DNA to produce cross-links. The platinum complex also can bind to nuclear and cytoplasmic protein. Cisplatin has black box warnings, including anaphylactic-like reactions, ototoxicity, and renal toxicity.

## Carboplatin

Carboplatin is a platinum alkylating agent that interferes with the function of DNA by producing interstrand DNA cross-links. It can be used in combination with paclitaxel for the treatment of bladder cancer, which is an off-label indication. Carboplatin has black box warnings, including bone marrow suppression, anaphylactic reactions, and vomiting.

## Ifosfamide (Ifex)

Ifosfamide is a nitrogen mustard alkylating agent that inhibits DNA and protein synthesis. Although not FDA approved for this indication, ifosfamide is often used as a treatment for metastatic bladder cancer.

## Thiotepa (Tepadina)

Thiotepa is an alkylating agent that inhibits DNA, RNA, and protein synthesis by producing cross-links between DNA strands. It is available as a powder for reconstitution and administration by injection. Thiotepa is indicated for the treatment of superficial papillary bladder cancer.

## **Antineoplastics, Anti microtubular**

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These agents prevent cell growth and proliferation. They work by enhancing tubulin dimers, as well as by stabilizing existing microtubules and inhibiting their disassembly.

## Docetaxel (Taxotere, Docefrez)

Docetaxel inhibits the depolymerization of tubulin, which inhibits DNA, RNA, and protein synthesis. It can be used for the treatment of bladder cancer, which is an off-label indication. It has several black box warnings, including bone marrow suppression, fluid retention, and hypersensitivity reactions. Its use is not recommended in certain patients with hepatic impairment. Patients receiving docetaxel treatment should be premedicated with corticosteroids the day before administration to help reduce fluid retention and hypersensitivity reactions.

## **PD-1/PD-L1 Inhibitors**

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PDL1 is expressed on the surface of activated T cells under normal conditions. PDL1 interaction inhibits immune activation and reduces T-cell cytotoxic activity when bound. This negative feedback loop is essential for maintaining normal immune responses and limits T-cell activity to protect normal cells during chronic inflammation. Tumor cells may circumvent T-cell–mediated cytotoxicity by expressing PDL1 on the tumor itself or on tumor-infiltrating immune cells, resulting in the inhibition of immune-mediated killing of tumor cells.

## Nivolumab (Opdivo)

Monoclonal antibody to programmed cell death ligand-1 protein (PDL1). It blocks the interaction between PDL-1 and its ligands. It is indicated for locally advanced or metastatic urothelial carcinoma in patients who have disease progression during or following platinum-containing chemotherapy, or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

## Avelumab (Bavencio)

Avelumab is an anti-PD-L1 IgG1 monoclonal antibody. It is indicated for locally advanced or metastatic urothelial carcinoma (UC) in patients who have disease progression during or following platinum-containing chemotherapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

## Pembrolizumab (Keytruda)

Monoclonal antibody to programmed cell death-1 protein (PD-1); blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is indicated as first-line treatment for locally advanced or metastatic urothelial carcinoma (UC) in patients who are not eligible for cisplatin-containing chemotherapy. It is also indicated for patients with disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Additionally, pembrolizumab is indicated for treatment of BCG-unresponsive, high-risk, nonmuscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors in patients who are ineligible for, or have elected not to undergo cystectomy. It is also indicated in combination with enfortumab vedotin for locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.

## Durvalumab (Imfinzi)

Indicated in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by single agent durvalumab as adjuvant treatment following radical cystectomy, for adults with muscle invasive bladder cancer.

## **FGFR Inhibitors**

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Fibroblast growth factor receptor (FGFR) regulate important biological processes including cell proliferation and differentiation, which are part of a complex signaling pathway in tumorigenesis.

## Erdafitinib (Balversa)

Erdafitinib inhibits FGFR phosphorylation and signaling, and thereby, decreases cell viability in cell lines expressing FGFR genetic alterations, including point mutations, amplifications, and fusions. It is indicated for locally advanced or metastatic urothelial carcinoma that has FGFR2 or FGFR3 genetic alterations and progressed during or following at least 1 line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

## **Anti-Nectin-4 Monoclonal Antibodies**

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Nectin-4 is a cell adhesion molecule that is expressed on many solid tumors.

## Enfortumab vedotin (Padcev, enfortumab vedotin-ejfv)

Enfortumab vedotin is an antibody-drug conjugate (ADC) composed of an anti-nectin-4 monoclonal antibody attached to the cell-killing agent, mono methylauristatin E (MMAE). Once the antibody attaches to nectin-4 that is expressed on the tumor, the complex is internalized in the lysosome, which releases MMAE. Enfortumab vedotin is indicated for locally advanced or metastatic urothelial cancer in patients who have received a PD-1/L1 inhibitor and platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic setting. It is also indicated in combination with pembrolizumab for locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.

## **Antineoplastics, Other**

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Nogapendekin alfa inbakicept is an interleukin-15 agonist. Binding of nogapendekin alfa inbakicept to its receptor results in proliferation and activation of NK, CD8+, and memory T cells without proliferation of immunosuppressive regulatory T cells (TREG).

## Nogapendekin alfa inbakicept (Anktiva)

Indicated for intravesical treatment in combination with BCG for adults with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.

## **Gene Therapies, Oncologics**

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Non-replicating adenoviral vector-based gene therapy delivers a copy of a gene encoding a human interferon-alfa 2b (IFNα2b) to bladder urothelium. Intravesical instillation results in cell transduction and transient local expression of IFNα2b protein that is anticipated to have antitumor effects.

## Nadofaragene firadenovec (Adstiladrin)

Indicated for high-risk Bacillus Calmette Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors. Instilled via bladder instillation every 3 months.

## **Bladder Cancer Doctor-Patient Conversation**

Doctor:  
"Thank you for coming in today. I have reviewed your test results, and they show that you have bladder cancer. I know this news can be overwhelming, but I want you to know we have a team ready to support you and discuss all your options."

Patient:  
"I appreciate your honesty. Can you tell me more about what type of bladder cancer I have and what stage it is?"

Doctor:  
"Of course. Your cancer is a non–muscle-invasive urothelial carcinoma, which means it is confined to the lining of your bladder and has not grown into the muscle wall. This stage generally has a good prognosis, and we have several effective treatment options."

Patient:  
"What are the treatment options, and what side effects should I expect?"

Doctor:  
"The standard first step is a procedure called transurethral resection of the bladder tumor, or TURBT, to remove the visible tumor. After that, we usually recommend intravesical therapy—medicine placed directly into the bladder, such as BCG or mitomycin. Common side effects include bladder irritation, urgency, and sometimes mild flu-like symptoms. If the cancer were to come back or not respond, we have other options, including different medicines, surgery, or even clinical trials for newer treatments."

Patient:  
"Will I need surgery to remove my bladder?"

Doctor:  
"At this stage, bladder removal is not necessary. We reserve that for cases where the cancer is high-risk, muscle-invasive, or not responding to other treatments. Our goal is to control the cancer while preserving your bladder and quality of life."

Patient:  
"How will treatment affect my daily life and work?"

Doctor:  
"Most people are able to continue many of their usual activities during treatment, though you may need to take time off for procedures or if you experience side effects. We’ll work together to manage any symptoms and adjust your care plan as needed."

Patient:  
"How often does bladder cancer come back, and what happens if it does?"

Doctor:  
"Bladder cancer has a high recurrence rate, so you’ll need regular follow-ups with cystoscopy and urine tests. If it comes back, we can repeat treatments or consider other therapies. We’ll monitor you closely and discuss all options at each step."

Patient:  
"Should I get a second opinion or consider clinical trials?"

Doctor:  
"Getting a second opinion is always your choice, and I can provide referrals if you like. Clinical trials are a good option for some patients, especially if standard treatments aren’t effective. I can help you explore those opportunities if you’re interested."

Patient:  
"Thank you for explaining everything. What should I do next?"

Doctor:  
"I’ll schedule your TURBT procedure and arrange a follow-up to discuss the results and next steps. Please write down any questions or concerns you think of, and bring a family member or friend for support if you’d like. We’re here to help you through this process."

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### **Renal cell carcinoma (RCC)**

Renal cell carcinoma (RCC) is the most common type of kidney cancer. RCC forms in tiny tubes inside your kidneys called tubules. Tubules direct substances your body needs, like water and nutrients, to your bloodstream, while filtering waste through your urine (pee). Up to 85% of kidney cancers are RCC.

RCC usually starts as a single clump of cancer cells — called a mass or a tumor — inside a single kidney. But you may have multiple tumors in one or both kidneys.

#### **Types of renal cell carcinoma**

Clear cell renal cell carcinoma (ccRCC) is the most common type of RCC. There are more than 50 types of RCC in addition to ccRCC. Many are rare. Scientists classify them based on various factors, including how tumor cells look under a microscope and their DNA, or genetic material.

More widely known types of RCC include:

* Clear cell renal cell carcinoma (ccRCC): Up to 85% of RCCs are clear cell renal carcinoma. ccRCC gets its name from the way tumor cells look underneath a microscope — clear-colored.
* Papillary renal cell carcinoma: Ten percent to 15% of RCCs are papillary renal cell carcinoma. It gets its name from the finger-like projections (papillae) visible on most tumors.
* Chromophobe renal cell carcinoma: Five percent to 10% of RCCs are chromophobe renal cell carcinoma. The cells are usually light-colored (like clear cell carcinoma) but tend to be larger.
* Unclassified RCC: Up to 6% of RCCs don’t fit into any category. Increasingly, scientists are discovering new ways to classify this undefined group of RCCs based on the microscopic characteristics of cancer cells, including cell DNA.

Your healthcare provider may refer to RCC as localized or advanced (metastatic). Localized RCC remains in your kidney and (in some cases) nearby surrounding structures. Metastatic RCC has spread to other parts of your body. Treatments and outcomes differ depending on which type you have.

#### **How common is renal cell carcinoma?**

Healthcare providers diagnose approximately 80,000 new cases of RCC each year in the U.S. and 400,000 new cases worldwide. Anyone can develop RCC, but it’s most common in men aged 60 to 80.

## **Symptoms and Causes**

Most people don’t notice symptoms in the early stages. When symptoms appear, they usually relate to how tumor growth impacts nearby tissue or organs.

Renal cell carcinoma symptoms include:

* Blood in your urine (hematuria).
* Pain in your flank (the sides of your body between your hips and ribs).
* A firm lump in your abdomen, low back or flank.
* Fever.
* Night sweats.
* Unexplained weight loss.

You may also experience symptoms of anemia, like shortness of breath and fatigue. Or you may experience symptoms of paraneoplastic syndromes. With paraneoplastic syndromes, tumors may release substances, like hormones, that cause changes in your body.

### **What causes renal cell carcinoma?**

RCC develops when abnormal cells multiply out of control inside kidney tubules. Exact causes are unknown. Still, scientists have discovered several risk factors that may make a person more likely to develop RCC.

#### **Risk factors**

Risk factors of renal cell carcinoma include:

* Smoking (the more you smoke, the greater your risk).
* Obesity (the higher your BMI, the greater your risk).
* High blood pressure (hypertension).
* Chronic kidney disease (which may include long-term dialysis treatment).
* Chronic hepatitis C infection.
* Long-term use of certain pain medicines (including NSAIDs and acetaminophen).
* Prior radiation therapy directed at your abdomen.
* Exposure to cancer-causing substances (carcinogens), like cadmium and asbestos.
* Sickle cell disease (associated with a rare form of RCC).
* Family history of kidney cancer.
* Genetic mutations (changes in your cell DNA).
* Tuberous sclerosis complex.
* Von Hippel-Lindau disease (VHL).

If you have a condition or a family history that puts you at risk of developing RCC, your healthcare provider may recommend regular screenings to catch tumors early.

## **Diagnosis and Tests**

Up to 25% of people with RCC don’t receive a diagnosis until the cancer’s more advanced. This is when symptoms usually become noticeable.

Increasingly, providers are catching tumors incidentally during unrelated imaging procedures before symptoms start. As a result, more people are receiving treatment in the early stages, when cancer responds best to treatment.

#### **Tests done to diagnose renal cell carcinoma**

Providers use imaging tests to identify tumors and plan treatment. The most common tests include:

* Ultrasound: A test that sends high-frequency sound waves through body tissues to create images displayed on a monitor. An ultrasound shows if tumors consist mostly of fluid (likely cysts) or solid material (more common in cancerous tumors).
* Computed tomography (CT) scan: A test that creates a series of images that show a detailed picture of the inside of your body. You’ll likely receive a scan before and after receiving a contrast (dye) injected into a vein. The dye travels to the tumor and shows it in detail.
* Magnetic resonance imaging (MRI): A test that uses a large magnet, radio waves and a computer to create detailed images of the inside of your body. You may need an MRI if you’re unable to have a CT scan (for example, if you’re allergic to the dye) or if the results of an ultrasound and CT scan are inconclusive.

While healthcare providers usually perform biopsies as a part of a cancer diagnosis, this isn’t often the case with renal cell carcinoma. During a biopsy, a provider removes a tumor tissue sample and uses a microscope to look for cancer cells.

Often, biopsies are too risky with RCC because they may cause kidney damage. Instead, providers examine tumor cells after they’ve removed the entire tumor as part of treatment. If imaging shows that cancer has spread, they may remove tumor cells from a location other than your kidney for testing.

Providers examine the cells to determine the specific type of RCC (if it’s unclear from imaging). Examining the cells also helps providers identify treatments that may work particularly well on that cancer type.

#### **Renal cell carcinoma staging**

Cancer staging helps your healthcare provider determine how advanced your cancer is. It can show if your cancer is localized or metastatic. This information helps your provider plan treatment. It also helps determine the likely outcomes of your treatment (prognosis).

Providers use the TNM (tumor, lymph node, metastasis) system to stage RCC. They assign a stage, ranging from I to IV. Stage I through Stage III cancers are localized, while stage IV is metastatic RCC.

* Stage I RCC: The tumor is smaller than 7 centimeters and hasn’t spread beyond your kidney.
* Stage II RCC: The tumor is larger than 7 centimeters and hasn’t spread beyond your kidney.
* Stage III RCC: The tumor may be any size. It has spread into nearby structures surrounding your kidney.
* Stage IV RCC: Cancer has spread outside of your kidney, to areas such as your lymph nodes and other organs.

##### **Where does renal cell carcinoma spread first?**

Metastatic RCC often spreads to your lymph nodes, lungs, bone, liver and brain. It can also spread to your ovaries or testicles.

## **Management and Treatment**

Treatment depends on many factors, including cancer stage and your overall health. Treatment for localized RCC is different from treatments for metastatic RCC.

#### **Localized renal cell carcinoma treatment**

Treatments include removing the cancer or destroying it using ablation techniques (destroying cells using extreme heat or cold).

Surgery is the most common treatment for localized RCC.

* Radical nephrectomy: Surgery that removes the affected kidney and some surrounding tissue, like lymph nodes or your adrenal glands (which may also contain cancer cells). Most people only need one healthy kidney.
* Partial nephrectomy: Surgery that removes only the affected part of your kidney. You may have a partial nephrectomy if you have a smaller tumor. A partial nephrectomy allows you to keep some kidney function. This is especially important if you don’t have two healthy kidneys.

If you’re not a candidate for surgery, your healthcare provider may recommend ablation procedures instead. These include:

* Cryotherapy: Freezing cancer cells to kill them.
* Radiofrequency ablation: Burning cancer cells to kill them.

#### **Metastatic renal cell carcinoma treatment**

Metastatic RCC treatments fight cancer cells throughout your body. You may still receive surgery to remove tumors, but that won’t be enough to eliminate metastatic cancer. Still, removing tumors may help with symptom relief, and surgery may allow you to delay starting other treatments.

The most common treatments include immunotherapy and targeted therapy. Depending on a variety of factors, these medications are either given as single agents or as combination therapy.

##### **Immunotherapy treatments**

Immunotherapy strengthens your immune system so it’s better at detecting and fighting cancer cells. Immunotherapy drugs include:

* Avelumab (Bavencio®).
* Ipilimumab (Yervoy®).
* Nivolumab (Opdivo®).
* Pembrolizumab (Keytruda®).

##### **Targeted therapy treatments**

Targeted therapy interferes with the process that allows cancer cells to multiply. This treatment restricts the blood supply to tumors, slowing their growth. Targeted therapy drugs include:

* Axitinib (Inlyta®).
* Bevacizumab (Avastin®).
* Cabozantinib (Cabometyx®).
* Everolimus (Afinitor®).
* Lenvatinib (Lenvima®).
* Pazopanib (Votrient®).
* Sorafenib (Nexavar®).
* Sunitinib (Sutent®).
* Temsirolimus (Torisel®).
* Tivozanib (Fotivda®).

Your healthcare provider may recommend other cancer treatments, including radiation therapy, depending on the cancer’s location, its severity and your response to other treatments.

## **Outlook / Prognosis**

It can be, but it depends on your specific diagnosis. People with localized RCC that’s been surgically removed generally have a very good long-term prognosis. People with higher-risk localized RCC may be offered immunotherapy after the cancer is removed to improve long-term outcomes.

There isn’t a cure for advanced RCC that’s spread beyond your kidney. Still, people with metastatic RCC are living longer as scientists discover better treatments targeting specific cancer cells.

### **What is the outlook for renal cell carcinoma?**

Increasingly, providers are detecting RCC in earlier stages, when the cancer is more treatable. Early detection and better treatments have increased the survival rate. The five-year survival rate for Stage I RCC is 90%. And while the life expectancy for people with Stage IV renal cell carcinoma was once a matter of months, many people are now living for several years.

## **Prevention**

Renal cell carcinoma isn’t always preventable, but you can reduce your risk. For example, choosing not to smoke (and quitting if you do) is one of the best things you can do to reduce your cancer risk.

## **Living With**

Talk to your healthcare provider about a care plan that can help you manage cancer symptoms and any treatment side effects. For example, some people will need to start dialysis treatment following surgery if one or more kidneys can’t do their job. It’s important to know how these treatments will impact you.

You may need help managing targeted therapy or immunotherapy side effects. Ask your healthcare provider what to expect before starting treatment.

**DIFFERENTIAL DIAGNOSIS**

Nearly 50% of renal cell carcinomas (RCCs) are found incidentally and the disease is generally asymptomatic. Thus, a possibility of RCC should be considered if a renal mass is found on a radiologic study.

The following conditions should be considered in a patient that presents with a renal mass as they can mimic the appearance of RCC:

* Abscess
* Angiomyolipoma (benign neoplasm)
* Renal oncocytoma (benign neoplasm)
* Renal adenoma (benign neoplasm)
* Renal lymphoma
* Renal cyst
* Renal infarction
* Sarcoma
* Metastasis from distant primary lesions e.g. Metastatic melanoma

Differential diagnoses based on the clinical findings would include:

* Acute pyelonephritis
* Bladder cancer
* Chronic pyelonephritis
* Non-Hodgkin lymphoma
* Adult type Wilms tumor

**EPIDEMIOLOGY**

There has been a steady increase in the incidence of renal cell carcinoma (RCC) since 1975 that has slowed in the past few years. This increase is attributed to the detection of asymptomatic and early cases due to advances and extensive use of imaging techniques. Over half of the RCC cases are detected incidentally. RCC accounts for over 3% of all adult malignancies and has several histological subtypes. The year 2020 estimates suggest that 73,750 cases of renal cancers will be detected (5% of all cancers in males and 3% of all cancers in females), and 14,830 persons will die from the disease. It is a tumor of the older age group and is most commonly seen between the ages of 60 to 70 years; it has an approximately 2 to 1 male to female ratio. As opposed to incidence mortality that has reduced by about 1% every year since 2008.

Overall 5-year relative survival in the US is 93% for patients diagnosed in the early stages of the disease. Early disease patients make up about two-thirds of all the cases diagnosed with renal cancer. The overall survival rate for kidney and renal pelvis cancers is 75%

### **What questions should I ask my doctor?**

What type of RCC do I have?  
RCC is classified into several types based on microscopic and molecular features. The most common subtypes are:

* Clear cell RCC (about 70% of cases): Characterized by cells with clear cytoplasm.
* Papillary RCC (10–15%): Further subclassification into type 1 and 2 is no longer recommended; these tumors are now grouped together.
* Chromophobe RCC (about 5%): Typically has the lowest risk of metastasis.
* Other rare types: Collecting duct carcinoma, oncocytic tumors, and several newly recognized molecularly defined RCCs.  
  Your pathology report will specify the exact type, which helps guide prognosis and treatment.

How advanced is my cancer?  
Advancement is described by stage (extent of spread) and grade (how abnormal the cells look). Staging is based on tumor size, lymph node involvement, and presence of metastases. Grading uses systems like the WHO/ISUP, which focuses on nuclear features. Your doctor will explain your stage (I–IV) and grade after reviewing imaging and pathology results.

What are the benefits and risks of potential treatments?

* Surgery: Mainstay for localized RCC (partial or radical nephrectomy). Benefits: potential cure for early-stage disease. Risks: bleeding, infection, loss of kidney function.
* Ablation or active surveillance: For small or slow-growing tumors in select patients.
* Targeted therapy and immunotherapy: Used for advanced/metastatic RCC. Benefits: can slow or shrink tumors. Risks: fatigue, high blood pressure, immune-related side effects, risk of infection.
* Radiation: Rarely used except for symptom control in metastatic disease.  
  Your care team will recommend options based on your cancer’s type, stage, and overall health.

What side effects or complications should I be aware of before receiving treatment?

* Surgery: Pain, risk of infection, bleeding, potential loss of kidney function.
* Targeted therapy/immunotherapy: Fatigue, diarrhea, high blood pressure, skin changes, immune-related complications.
* Ablation: Risk of bleeding, infection, or damage to nearby structures.  
  Discuss all potential side effects with your team before starting treatment.

How often will I need follow-up visits following treatment?  
Follow-up depends on your cancer’s stage and treatment. Typically, you’ll have imaging and lab tests every 3–12 months for the first few years, then less frequently over time. The goal is to monitor for recurrence or new tumors.

What lifestyle changes should I expect during treatment?

* You may need to adjust activity during recovery from surgery.
* Maintain a healthy diet and stay physically active as tolerated.
* Avoid tobacco and limit alcohol.
* Manage blood pressure and other chronic conditions.  
  Your team will provide specific recommendations based on your treatment plan and overall health.

What’s my prognosis?  
Prognosis depends on cancer type, stage, grade, and your overall health. Five-year survival rates are high for localized disease (over 80% for clear cell, papillary, and chromophobe RCC), but lower for advanced or metastatic disease (as low as 44% for collecting duct carcinoma, and lower for sarcomatoid features). Your doctor will give you personalized information based on your case.

## 

## **Genomic Data in Renal Cell Carcinoma (RCC)**

## Key Genomic Alterations by RCC Subtype

Clear Cell RCC (ccRCC):

* The most common subtype of RCC.
* Frequently mutated genes:
  + VHL (Von Hippel-Lindau): Inactivated in the majority of ccRCC cases; central to tumor development and a target for VEGF and mTOR inhibitor therapies.
  + PBRM1, BAP1, SETD2: Mutated in a significant proportion of ccRCC; these mutations can influence prognosis and treatment response.
  + Other less frequent mutations: CSF1R, NPM1, EGFR, NOTCH1.
  + Prognostic impact: BAP1 mutations are often linked to worse outcomes, while PBRM1 mutations may be associated with better prognosis.

Papillary RCC (pRCC):

* Commonly associated with mutations in the MET gene, particularly in hereditary forms.
* Other mutations: PAX8, CDKN2A/B, FANCC, FGFR4, PIK3C, PTPRS, SMARCB1, TERT.
* MET-targeted therapies are being explored for pRCC.

Chromophobe RCC (chRCC):

* Distinct mutation profile compared to ccRCC and pRCC.
* Common mutations: ASXL2, BRCA1, CDH1, CDKN2A/B/C, DNMT1, EP300.

## Hereditary RCC Syndromes and Germline Mutations

* Von Hippel-Lindau (VHL) disease: Germline VHL mutations; associated with bilateral, multifocal ccRCC, pheochromocytoma, and other tumors.
* Hereditary Papillary Renal Carcinoma (HPRC): Germline MET mutations; leads to bilateral, multifocal pRCC.
* Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC): Germline FH mutations.
* Birt-Hogg-Dubé Syndrome (BHD): Germline FLCN mutations; associated with chromophobe and oncocytic tumor

## 

## **Doctor-Patient Conversation for Renal Cell Carcinoma (RCC)**

Doctor:  
"Thank you for coming in today. I have reviewed your imaging and lab results, and they show that you have renal cell carcinoma, which is a type of kidney cancer. I know this is a lot to take in, and I want you to know that our team will support you through every step."

Patient:  
"I’m shocked. I don’t really have any symptoms—how did this happen?"

Doctor:  
"That’s very common. Many people with RCC don’t have symptoms early on, and we often find it by chance during scans for other reasons. When symptoms do appear, they can include blood in the urine, pain in the side, or a mass in the abdomen, but most cases are caught before that."

Patient:  
"What kind of tests do I need next?"

Doctor:  
"We’ll need some additional imaging, like a CT or MRI, to see if the cancer has spread and to help us plan treatment. We’ll also check your blood and kidney function. Sometimes, we recommend genetic testing, especially if there’s a family history of kidney cancer or if you’re younger than most people who get this disease."

Patient:  
"What are my treatment options?"

Doctor:  
"For most people with early-stage RCC, surgery to remove the tumor is the main treatment and can often be curative. If the tumor is small, we may be able to remove just part of the kidney. For larger or more advanced cancers, we might need to remove the whole kidney, and sometimes use targeted therapy or immunotherapy if the cancer has spread. We’ll tailor the plan to your specific situation."

Patient:  
"What are the risks or side effects of treatment?"

Doctor:  
"Surgery can cause pain, risk of infection, bleeding, and sometimes reduced kidney function. Targeted therapies and immunotherapies can cause fatigue, high blood pressure, diarrhea, or immune-related side effects. We’ll discuss all of this in detail and support you in managing any side effects."

Patient:  
"How often will I need follow-up after treatment?"

Doctor:  
"After surgery or other treatments, you’ll have regular follow-up visits and imaging every few months at first, then less often over time, to make sure the cancer hasn’t come back or spread."

Patient:  
"Is there anything I can do to help myself during treatment?"

Doctor:  
"Staying active, eating a healthy diet, and managing other health conditions like blood pressure are important. We’ll connect you with a nutritionist or support services as needed. Please let us know if you have any concerns or need help coping—emotional support is a key part of your care."

Patient:  
"Thank you for explaining everything."

Doctor:  
"You’re welcome. Please write down any questions you have, and bring a family member or friend to your next appointment if you’d like. We’ll work together to make the best plan for you

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**MERKEL CELL CARCINOMA(SKIN)**

**DEFINITION AND DESCRIPTION**

Merkel cell carcinoma is a rare type of skin cancer. It most often appears as a bump on the face, head or neck. Merkel cell carcinoma also is called neuroendocrine carcinoma of the skin.

Merkel cell carcinoma most often happens in people older than 50. Long-term sun exposure or a weakened immune system may raise the risk of getting this cancer.

Merkel cell carcinoma tends to grow fast and to spread quickly to other parts of the body. Treatment may depend on whether the cancer has spread beyond the skin.

**Causes**

It's often not clear what causes Merkel cell carcinoma.

This skin cancer happens when cells in the skin develop changes in their DNA. A cell's DNA holds the instructions that tell the cell what to do. In healthy cells, the DNA gives instructions to grow and multiply at a set rate. The instructions tell the cells to die at a set time.

In cancer cells, the DNA changes give other instructions. The changes tell the cancer cells to grow and multiply at a fast rate. Cancer cells can keep living when healthy cells die. This causes too many cells.

The cancer cells might form a mass called a tumor. The tumor can grow to invade and destroy healthy body tissue. In time, cancer cells can break away and spread to other parts of the body. When cancer spreads, it's called metastatic cancer.

Merkel cell carcinoma is named for the cells where experts once thought it started. The Merkel cells are found at the bottom of the outer layer of skin. The Merkel cells are connected to the nerve endings in the skin that play a role in the sense of touch. Healthcare professionals no longer believe that this cancer starts in the Merkel cells. They don't know exactly what kind of cells it starts in.

It's often not clear what causes the DNA changes that lead to Merkel cell carcinoma. Researchers have found that a common virus plays a role in causing Merkel cell carcinoma. The virus, called Merkel cell polyomavirus, lives on the skin. It doesn't cause symptoms. Experts don't know exactly how this virus causes Merkel cell carcinoma.

**Risk factors**

Factors that may raise the risk of Merkel cell carcinoma include:

* **Skin that sunburns easily.** Anyone of any skin color can get Merkel cell carcinoma. But it's more common in people who have less melanin in their skin. Melanin is a substance that gives color to skin. It also helps protect the skin from damaging rays from the sun.  
  People with Black or brown skin have more melanin than do people with white skin. So white people are more likely to get Merkel cell carcinoma than are people with Black or brown skin.
* **Too much UV light.** Ultraviolet light, also called UV light, raises the risk of Merkel cell carcinoma. UV light can come from the sun. Being in the sun without covering the skin with clothing or sunblock raises the risk of Merkel cell carcinoma. UV light for treatment of the skin condition psoriasis also can raise the risk of this skin cancer.
* **Tanning bed use.** People who use indoor tanning beds have a higher risk of Merkel cell carcinoma.
* **A weakened immune system.** People with weakened immune systems are more likely to get Merkel cell carcinoma. A weakened immune system can happen in people with certain health conditions, such as HIV infection and chronic leukemia. It also can happen in people taking certain medicines, such as medicines that lower the immune response.
* **History of other skin cancers.** Merkel cell carcinoma is linked to other skin cancers, such as basal cell carcinoma and squamous cell carcinoma.
* **Older age.** The risk of Merkel cell carcinoma goes up with age. This cancer is most common in people older than age 50, though it can happen at any age.

**Symptoms**

The first symptom of Merkel cell carcinoma most often is a growth on the skin. This skin cancer can happen anywhere on the body. It happens most often on skin that typically gets sunlight. In white people, the growth is most likely to be on the head or neck. In Black people, the growth more often is on the legs.

A Merkel cell carcinoma can cause:

* A bump on the skin that often is painless.
* A bump that grows quickly.
* A bump whose two sides don't match.
* A bump that looks pink, purple, red-brown, or the same color as the skin around it.

### 

### **When to see a doctor**

Make an appointment with a healthcare professional if you have a mole, freckle or bump that changes size, shape or color. Also see a healthcare professional if you have a bump that grows fast or bleeds easily after minor injury, such as washing your skin or shaving.

## **Diagnosis**

Merkel cell carcinoma diagnosis often starts with an exam. A healthcare professional may look at your skin and remove a sample of cells for testing. This skin cancer may be hard to diagnose because it may look like other skin growths.

### **Physical exam**

During a physical exam, a healthcare professional looks at your skin for moles, freckles and other growths.

### **Biopsy**

A biopsy is a procedure to remove a sample of tissue for testing in a lab. For Merkel cell carcinoma, a healthcare professional may use a tool to cut away some of the concerning skin. Other ways to do a skin biopsy involve using a shaving tool or a circular cutting tool to get some of the skin. The sample is tested in a lab to see if it is cancer.

### **Tests for cancer that spreads**

Your healthcare professional may use other tests to find out whether the cancer has spread beyond your skin. These other tests may include:

* **Sentinel node biopsy.** A sentinel node biopsy is a procedure to see whether cancer has spread to the lymph nodes. This procedure involves putting a dye into the skin near the cancer. The dye then flows through the lymphatic system to the lymph nodes.  
  The first lymph nodes that get the dye are called the sentinel nodes. A healthcare professional removes these lymph nodes and looks for cancer cells under a microscope.
* **Imaging tests.** Imaging tests used to look for signs that the cancer has spread include a chest X-ray, a CT scan of the chest and belly, and a positron emission tomography scan, also called a PET scan.

**Treatment**

Treatment for Merkel cell carcinoma most often involves surgery to remove the cancer. If the cancer has spread beyond the skin, treatment may involve medicines or radiation.

### **Surgery**

A surgeon removes the cancer along with a border of skin that doesn't have cancer. For cancer that has spread to lymph nodes near the skin cancer, the surgeon removes those lymph nodes. This is called a lymph node dissection.

Surgery most often involves a scalpel to cut away the cancer. Sometimes, a surgeon may use a procedure called Mohs surgery.

Mohs surgery involves cutting away thin layers of skin. The surgeon uses a microscope to look at each layer for cancer. The process keeps going until there's no more cancer. The goal of Mohs surgery is to remove all the cancer without harming the healthy skin around it.

### **Radiation therapy**

Radiation therapy treats cancer with powerful energy beams. For Merkel cell carcinoma, a healthcare professional may use radiation therapy after surgery to destroy cancer cells that remain. Radiation may be the only treatment for people who don't want to have surgery. Radiation also can treat cancer that has spread.

### **Immunotherapy**

Immunotherapy for cancer is a treatment with medicine that helps the body's immune system kill cancer cells. The immune system fights off diseases by attacking germs and other cells that shouldn't be in the body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells.

Most often, immunotherapy treats Merkel cell carcinoma that comes back after treatment or spreads to other areas of the body.

### **Chemotherapy**

Chemotherapy treats cancer with strong medicines. Healthcare professionals don't often use chemotherapy to treat Merkel cell carcinoma. But your healthcare team may suggest it if your Merkel cell carcinoma spreads to your lymph nodes or other organs, or if it returns after treatment.

For Merkel cell carcinoma, questions might include:

* What is likely causing my symptoms or condition?
* Are there other possible causes for my symptoms or condition?
* What tests do I need?
* What treatments are there?
* I have other health conditions. How can I best manage them together?

**Complications**

Even with treatment, Merkel cell carcinoma often spreads to other parts of the body. When cancer spreads, healthcare professionals sometimes say it metastasizes. Merkel cell carcinoma tends to travel first to nearby lymph nodes.

Later it may spread to the brain, bones, liver or lungs. It can keep these organs from working as they should. Cancer that spreads is harder to treat and can be fatal.

**Prevention**

While exposure to sunlight isn't proved to cause all Merkel cell carcinomas, it is thought to be a risk factor for this cancer. Getting less sun exposure may lower your risk of skin cancer.

Try to:

### **Stay out of the sun in the middle of the day**

For much of North America, the sun's rays are strongest between about 10 a.m. and 3 p.m. Plan to be outdoors at other times of the day, even during winter or when the sky is cloudy. When outside, stay in the shade as much as possible.

### **Wear sunscreen year-round**

Use a broad-spectrum sunscreen with an SPF of at least 30, even on cloudy days. Apply sunscreen generously. Reapply every two hours, or more often if you're swimming or sweating.

### **Wear protective clothing**

To protect your skin from the sun, wear dark, tightly woven clothes that cover the arms and legs. Wear a wide-brimmed hat that shades the face and ears.

Don't forget sunglasses. Look for sunglasses that block both types of ultraviolet light, also called UV light, that comes from the sun. The two types are UVA and UVB.

### **Check your skin often**

Look at your skin often for new growths or changes in moles, freckles, bumps and birthmarks. Use mirrors to check your face, neck, ears and scalp. Report any changes to your healthcare professional.

Even though Merkel cell carcinoma most often is on the face, head and neck, look at other areas of your body. Look at your chest and trunk and the tops and undersides of your arms and hands. Look at the front and back of your legs and your feet. Look at the bottom of the feet and the spaces between your toes. Also check your genital area and between your buttocks.

## **Outlook / Prognosis**

Merkel cell carcinoma often returns after treatment. You may need to see your healthcare provider every three to four months for the first several years and get imaging scans to check for cancer recurrence.

Many factors — like your overall health, age and cancer stage — influence survival rates when you have Merkel cell carcinoma. Experts estimate that 3 out of 4 people who have localized Merkle cell carcinoma (cancer that hasn’t spread) are alive five years after diagnosis. That number drops to 1 in 4 when you have metastatic cancer. There are many clinical trials underway for new treatments for Merkel cell carcinoma.

## **QUESTION AND ANSWERS SET**

## What caused Merkel cell carcinoma?

Merkel cell carcinoma (MCC) is most often linked to two main factors: exposure to ultraviolet (UV) radiation (from sunlight or tanning beds) and infection with the Merkel cell polyomavirus (MCV). UV radiation damages the DNA in skin cells, increasing cancer risk. MCV is a common virus found in most MCC tumors, but most people infected with MCV never develop this cancer. Other important risk factors include having fair skin, being over age 50, being male, a weakened immune system (from conditions like HIV, chronic leukemia, organ transplant, or immunosuppressive medications), and a history of other skin cancers.

## What’s the best treatment for me?

The best treatment depends on the stage and location of your MCC, your overall health, and personal preferences. Treatment usually involves surgical removal of the tumor, often followed by radiation therapy to reduce the risk of recurrence. For more advanced cases, immunotherapy (such as immune checkpoint inhibitors) or chemotherapy may be recommended. Your care team will tailor a plan based on your specific situation and discuss the risks and benefits of each option.

## What steps can I take to prevent cancer recurrence (return)?

* Protect your skin from UV exposure: Use sunscreen, wear protective clothing, and avoid tanning beds.
* Monitor your skin: Perform regular self-exams and attend all follow-up appointments for early detection of recurrence.
* Maintain a healthy immune system: Manage chronic conditions, avoid unnecessary immunosuppression, and follow your doctor’s advice.
* Report new symptoms: Notify your healthcare provider promptly if you notice new lumps, skin changes, or swollen lymph nodes.

## Should I look for signs of complications?

Yes. MCC can recur or spread (metastasize) even after treatment, often first to nearby lymph nodes and later to other organs like the brain, bones, liver, or lungs. Watch for:

* New or growing lumps near the original cancer site or elsewhere
* Unexplained pain, swelling, or changes in your skin
* Persistent cough, headaches, or neurological symptoms

Report any of these to your healthcare team immediately, as early intervention can improve outcome

**DIFFERENTIAL DIAGNOSIS**

* Basal cell carcinoma
* Cutaneous melanoma
* Cutaneous squamous cell carcinoma
* Dermatofibroma
* Keratoacanthoma
* The dermatologic manifestation of metastatic carcinomas

## **Epidemiology**

### Frequency

Since Merkel cell carcinoma (MCC) was first described in 1972, more than 600 cases have been reported in the literature; over 320 of these cases have involved the head and neck.

The reported annual incidence of Merkel cell carcinoma (MCC) is 0.2-0.45 cases per 100,000 population. This rare cancer occurs 100 times less frequently than melanoma.

Evidence suggests that the incidence of Merkel cell carcinoma (MCC) is increasing. In an analysis of the Surveillance, Epidemiology and End Results (SEER) database, Hodgson (2005) reported that the incidence of Merkel cell carcinoma (MCC) increased 3-fold between 1986 and 2001.Moreover, a study by Uitentuis et al reported that in the Netherlands, between 1993 and 2016, the incidence of Merkel cell carcinoma (MCC) rose from 0.17 per 100,000 person-years to 0.59 per 100,000 person-years

S**TAGING**

* Stage I - Absence of lymphadenopathy
  + Stage IA - Tumors < 2 cm
  + Stage IB - Tumors >2 cm
* Stage II - Positive regional lymphadenopathy
* Stage III - Evidence of distant metastases

At presentation, most patients have stage I disease (55%), followed by stage II (31%), and stage III (6%).

## **Doctor-Patient Conversation for Merkel Cell Carcinoma (MCC)**

Doctor:  
"Thank you for coming in today. I have reviewed your biopsy and imaging results, and they show that you have Merkel cell carcinoma, which is a rare and aggressive type of skin cancer. I know this is a lot to process, and I want you to know that we have a team ready to support you at every step."

Patient:  
"I’ve never heard of this cancer before. How sure are you about the diagnosis?"

Doctor:  
"We’re confident in the diagnosis. The pathology tests, including special markers, confirm it’s Merkel cell carcinoma. However, if you’d like, we can arrange for a second opinion or review by another specialist."

Patient:  
"Has the cancer spread? What tests will I need?"

Doctor:  
"To determine if the cancer has spread, we recommend additional tests such as a sentinel lymph node biopsy and scans like CT or PET-CT. These will help us stage the cancer and decide on the best treatment plan."

Patient:  
"What are my treatment options?"

Doctor:  
"Treatment usually starts with surgery to remove the tumor, sometimes followed by radiation therapy to lower the risk of recurrence. If the cancer has spread or is at high risk, we may recommend immunotherapy. We’ll tailor the plan based on your stage, overall health, and preferences."

Patient:  
"What are the side effects, and how will treatment affect my daily life?"

Doctor:  
"Surgery may leave a scar and can require some recovery time. Radiation can cause skin irritation and fatigue. Immunotherapy can cause fatigue and, less commonly, immune-related side effects. Most people are able to continue many of their usual activities, but we’ll work together to manage any side effects and support your quality of life."

Patient:  
"What are the chances that the cancer will come back? How will I be monitored?"

Doctor:  
"Merkel cell carcinoma can come back, so close follow-up is important. You’ll have check-ups every three months for the first few years, then less often. We’ll do physical exams and, if needed, scans to catch any recurrence early."

Patient:  
"Are there any clinical trials I should consider?"

Doctor:  
"There are clinical trials for MCC, especially if standard treatments aren’t effective or if you have advanced disease. I can help you explore these options and answer any questions about what participation would involve."

Patient:  
"Is there support available for me and my family?"

Doctor:  
"Yes, there are support groups and counseling services for people with Merkel cell carcinoma and their families. I can connect you with these resources, and our team is always here to answer questions and provide support."

Patient:  
"Thank you for explaining everything."

Doctor:  
"You’re welcome. Please write down any questions you think of, and bring a family member or friend to your next appointment if you’d like. We’re here to help you through this process."

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**NASOPHARYNGEAL CANCER**

**DEFINITION AND DESCRIPTION**

Nasopharyngeal carcinoma is cancer that starts as a growth of cells in the nasopharynx. The nasopharynx is the upper part of the throat. It sits behind the nose.

Nasopharyngeal (nay-zoh-fuh-RIN-jee-ul) carcinoma is rare in the United States. It happens much more often in other parts of the world, mainly Southeast Asia.

Nasopharyngeal carcinoma is hard to find early. That's most likely because the nasopharynx isn't easy to examine. And there may be no symptoms at first.

Treatment for nasopharyngeal carcinoma usually involves radiation therapy, chemotherapy or a mix of the two. Work with your healthcare professional to find the approach that's right for you.

**Causes**

The exact cause of nasopharyngeal carcinoma often isn't known.

Nasopharyngeal carcinoma is a kind of cancer that starts in the upper part of the throat, called the nasopharynx. It happens when cells in the nasopharynx develop changes in their DNA. A cell's DNA holds the instructions that tell the cell what to do. In healthy cells, the DNA gives instructions to grow and multiply at a set rate. The instructions tell cells to die at a set time.

In cancer cells, the DNA changes give different instructions. The changes tell the cancer cells to make many more cells quickly. Cancer cells can keep living when healthy cells would die. This causes too many cells.

The cancer cells might form a growth called a tumor. The tumor can grow to invade and destroy healthy body tissue. In time, cancer cells can break away and spread to other parts of the body. When cancer spreads, it's called metastatic cancer.

**Risk factors**

Researchers have found some factors that seem to raise the risk of getting nasopharyngeal carcinoma. They include:

* **Certain ancestries.** Nasopharyngeal carcinoma is more common in parts of China, Southeast Asia, northern Africa and the Arctic. People who live in these areas or have ancestry that comes from these parts of the world may have an increased risk of nasopharyngeal carcinoma.
* **Middle age.** Nasopharyngeal carcinoma can occur at any age. But most often it's diagnosed in adults between the ages of 30 and 60.
* **Salt-cured foods.** Chemicals released in steam when cooking salt-cured foods might raise the risk of nasopharyngeal carcinoma. The steam from foods such as fish and preserved vegetables may enter the nose during cooking. Contact with these chemicals at an early age may raise the risk even more.
* **Epstein-Barr virus.** This common virus most often causes mild symptoms like those of a cold. Sometimes it can cause infectious mononucleosis. The Epstein-Barr virus also is linked to some cancers, including nasopharyngeal carcinoma.
* **Family history.** Having a family member with nasopharyngeal carcinoma raises the risk of the disease.
* **Alcohol and tobacco.** Heavy alcohol intake and tobacco use can raise your risk of nasopharyngeal carcinoma.

**Symptoms**

Nasopharyngeal carcinoma may not cause signs or symptoms at first. When it does cause symptoms, they might include:

* A lump in your neck caused by a swollen lymph node.
* Bleeding from the nose.
* Bloody saliva.
* Double vision.
* Ear infections.
* Facial numbness.
* Headaches.
* Hearing loss.
* Nasal stuffiness.
* Ringing in the ears, called tinnitus.
* Sore throat.

### **When to see a doctor**

Make an appointment with a doctor or other healthcare professional if you have any symptoms that worry you.

## **Diagnosis**

Nasopharyngeal carcinoma diagnosis often begins with an exam by a healthcare professional. The health professional may use a special scope to look inside the nasopharynx for signs of cancer. To confirm the diagnosis, a sample of tissue might be removed for testing.

### **Physical exam**

A healthcare professional may do a physical exam to look for signs of cancer. This might include looking in your nose and throat. The health professional also may feel your neck for swelling in the lymph nodes. The health professional may ask about your symptoms and your habits.

### **Endoscopy**

A healthcare professional who suspects nasopharyngeal carcinoma may do a procedure called a nasal endoscopy.

This test uses a thin, flexible tube with a tiny camera on the end, called an endoscope. It lets your healthcare professional see inside your nasopharynx. The endoscope might go through your nose to see your nasopharynx. Or the endoscope might go through the opening in the back of your throat that leads up into your nasopharynx.

### **Biopsy**

A biopsy is a procedure to remove a sample of tissue for testing in a lab. For nasopharyngeal carcinoma, a healthcare professional might take the sample during a nasal endoscopy procedure. To do this, the health professional puts special tools through the endoscope to remove some tissue. If there is swelling in the lymph nodes in the neck, a needle might be used to draw out some cells for testing.

### **Tests to find the extent of the cancer**

Once the diagnosis is confirmed, other tests can find the extent, called the stage, of the cancer. These might include imaging tests such as:

* CT scan.
* MRI scan.
* Positron emission tomography scan, also called a PET scan.
* X-ray.

The stages of nasopharyngeal carcinoma range from 0 to 4. A lower number means the cancer is small and is mostly in the nasopharynx. As the cancer grows larger or spreads beyond the nasopharynx, the stages go up.

A stage 4 nasopharyngeal carcinoma can mean the cancer has grown into nearby structures, such as the area around the eye or the lower parts of the throat. Stage 4 also can mean the cancer has spread to the lymph nodes or other parts of the body.

Your healthcare team uses the stage and other factors to plan your treatment and understand the likely course of the cancer, called the prognosis.

**Treatment**

Treatment for nasopharyngeal carcinoma most often begins with radiation therapy or a mix of radiation and chemotherapy.

You and your healthcare team work together to make a treatment plan. Several factors go into making the plan. These may include the stage of your cancer, your treatment goals, your overall health and the side effects you're willing to have.

### **Radiation therapy**

Radiation therapy treats cancer with powerful energy beams. The energy can come from X-rays, protons or other sources.

Radiation therapy for nasopharyngeal carcinoma most often involves external beam radiation. During this procedure, you lie on a table. A large machine goes around you. It sends radiation to the precise spot where it can target your cancer.

For small nasopharyngeal carcinomas, radiation therapy may be the only treatment needed. For cancers that are larger or have grown into nearby areas, radiation therapy is typically combined with chemotherapy.

For nasopharyngeal carcinoma that returns, you might have a type of internal radiation therapy, called brachytherapy. With this treatment, a healthcare professional puts radioactive seeds or wires in the cancer or close to it.

### **Chemotherapy**

Chemotherapy treats cancer with strong medicines. Most chemotherapy medicines are given through a vein. Some come in pill form.

Chemotherapy may be given at the same time as radiation therapy to treat nasopharyngeal carcinoma. It also may be used before or after radiation therapy.

### **Immunotherapy**

Immunotherapy for cancer is a treatment with medicine that helps the body's immune system kill cancer cells.

The immune system fights off diseases by attacking germs and other cells that shouldn't be in the body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells.

For nasopharyngeal carcinoma, immunotherapy might be an option if the cancer comes back or spreads to other parts of the body.

### **Surgery**

Surgery is not often used as a first treatment for nasopharyngeal carcinoma. But you might have surgery to remove cancerous lymph nodes in the neck.

Sometimes, surgery may be used to remove cancer from the nasopharynx. Or it might treat cancer that comes back after having radiation or chemotherapy. To get to the cancer, a surgeon may make a cut in the roof of the mouth or in the face near the nose. Sometimes the surgeon can remove the cancer using special surgical tools that go through the nose.

**Lifestyle and home remedies**

### **Coping with dry mouth**

Radiation therapy for nasopharyngeal carcinoma often causes dry mouth. Dry mouth may last a long time after treatment. For some people, it doesn't go away.

Dry mouth can cause discomfort. It also can lead to infections in your mouth. It can make it hard to eat, swallow and speak. And it can affect the health of your teeth. Ask your healthcare professional about seeing a dentist if you have dry mouth complications.

To help ease dry mouth and its complications:

* **Brush your teeth a few times each day.** Use a soft-bristled toothbrush. Brush gently. Tell your healthcare team if gentle brushing hurts your mouth.
* **Rinse your mouth with a solution after meals.** Ask your healthcare team what solution to use.
* **Keep your mouth moist with water or sugarless candies.** Drink water throughout the day to keep your mouth moist. Also try ice chips, sugarless gum or sugarless candies to help your mouth make saliva.
* **Choose moist foods.** Don't eat dry foods. Moisten food with sauce, gravy, broth, butter or milk.
* **Don't eat acidic or spicy foods and drinks.** Choose foods and drinks that won't irritate your mouth. Don't drink caffeinated and alcoholic beverages.

Tell your healthcare team if you have dry mouth. There may be treatments to help you cope with more-severe symptoms of dry mouth. Your healthcare team also may send you to an expert in nutrition, called a dietitian. A dietitian can help you find foods that are easier to eat with dry mouth.

**Complications**

Nasopharyngeal carcinoma complications can include:

* **Cancer that grows into nearby structures.** Advanced nasopharyngeal carcinoma can grow large enough to go into nearby structures, such as the throat, bones and brain.
* **Cancer that spreads to other areas of the body.** Nasopharyngeal carcinoma often spreads beyond the nasopharynx. It typically spreads to the lymph nodes in the neck first. When it spreads to other parts of the body, nasopharyngeal carcinoma most often goes to the bones, lungs and liver.

**Prevention**

There's no sure way to prevent nasopharyngeal carcinoma. But, if you're worried about your risk of this cancer, think about giving up habits that have been linked with the disease. For instance, don't use tobacco. You may choose to cut back on or not eat salt-cured foods.

### **Tests to screen for nasopharyngeal carcinoma**

In the United States and in other areas where the disease is rare, there's no routine screening for nasopharyngeal carcinoma.

In places where nasopharyngeal carcinoma is much more common, such as some areas of China, people at high risk of the disease may have screening. Screening may involve blood tests to detect the Epstein-Barr virus.

## **Outlook / Prognosis**

NPC can be cured if healthcare providers diagnose the condition before it spreads.

#### **What is the survival rate for nasopharyngeal cancer?**

Data kept by the American Cancer Society show 63% of people with nasopharyngeal cancer in the U.S. were alive five years after diagnosis. Like many cancer types, NPC survival rates improve if cancer is diagnosed before it can spread:

* Local: An estimated 82% of people with local nasopharyngeal cancer were alive five years after diagnosis. Local NPC is cancer that hasn’t spread to other areas of your body.
* Regional disease: An estimated 72% of people with regional nasopharyngeal cancer were alive five years after diagnosis. This is cancer in nearby lymph nodes, tissues and organs.
* Metastatic disease: An estimated 49% of people with cancer that’s spread (metastasized) to more distant organs were alive five years after diagnosis.

Survival rates are estimates based on the experiences of other people who have the same kind of cancer. Many factors affect survival rates, including a person’s age, overall health and how well they respond to treatment.

If you have nasopharyngeal cancer, it’s important to remember that your experience may be different from other people’s experiences. Ask your healthcare provider what you can expect given your situation.

## **Living WITH**

Your healthcare provider can help you find ways to manage your symptoms, relieve pain and improve your overall quality of life. Recommendations often include:

* Eating a healthy, well-balanced diet.
* Practicing mindfulness or meditation.
* Joining a local support group.
* Has the cancer spread to other areas of my body?
* What stage of nasopharyngeal cancer do I have?
* What are my treatment options?
* What side effects are possible from treatment?
* Can treatment cure my cancer?
* How long will my treatment last?
* What are the chances that my cancer will come back?
* What will my follow-up care involve?

**QUESTIONS AND ANSWERS SET**

## What tests do I need?

* A physical exam focusing on the nose, throat, neck, and lymph nodes.
* Nasal endoscopy (nasopharyngoscopy) to look inside the nasopharynx with a flexible scope.
* Biopsy during endoscopy to remove tissue for cancer confirmation.
* Imaging tests such as CT scan, MRI scan, and PET-CT scan to determine the extent and spread of cancer.
* Additional tests depending on symptoms, such as hearing tests, dental exams, eye exams, and blood tests for Epstein-Barr virus (EBV) levels.
* Other possible tests include chest X-ray or barium swallow if symptoms warrant.

## Do I need to do anything to prepare for these tests?

* Preparation varies by test; for example, imaging scans may require fasting or avoiding metal objects.
* Your healthcare provider will give specific instructions for each test.
* Generally, no extensive preparation is needed for physical exams or endoscopy, but you should inform your doctor about all medications and health conditions.

## Are there other possible causes for these symptoms?

* Yes, symptoms like nasal congestion, hearing loss, or neck lumps can be caused by infections, benign growths, or other non-cancerous conditions.
* Your doctor will evaluate your symptoms and history to rule out other causes before confirming NPC.

## I have other health issues. How will this affect them?

* Other health conditions may influence treatment choices and side effect management.
* Discuss all your health issues with your doctor so they can tailor treatment and monitor interactions or complications.
* Supportive care such as nutritional, dental, or speech therapy may be needed depending on your overall health.

## What treatment do you suggest?

* Treatment depends on the stage and extent of cancer.
* Common treatments include radiation therapy and chemotherapy.
* Sometimes a combination of both is used.
* Early-stage NPC may be curable with radiation alone.
* Palliative care may be recommended to manage symptoms and side effects during treatment.

## Is my cancer likely to return?

* Recurrence risk depends on cancer stage, treatment effectiveness, and individual factors.
* Your doctor will discuss your prognosis and follow-up plan.
* Regular monitoring after treatment is important to catch any recurrence early.

## Are there clinical trials I might get into?

* Clinical trials may be available and could offer access to new treatments.
* Ask your healthcare team about ongoing trials suitable for your condition and eligibility

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for nasopharyngeal carcinoma includes the following:

Benign Conditions

* Nasopharyngeal polyposis
* Angiofibromas
* Antro-choanal polyp
* Inverting papilloma
* Adenoid hypertrophy
* Thornwaldt cyst
* Encephalocele

Malignant Lesions

* Lymphoma
* Sarcoma
* Mucosal melanomas

**EPIDEMIOLOGY**

NPC is endemic to southern China, Southeast Asia, and Africa. The rate varies from a minuscule value of less than 1 per 100,000 individuals in non-endemic areas to a high of 25 to 50 cases per 100,000 males and 15 to 20 cases per 100,000 individuals in females in endemic regions

## **Doctor-Patient Conversation: Nasopharyngeal Carcinoma**

Doctor: Good morning. I have reviewed your test results, including the biopsy and imaging, and I want to discuss what we found.

Patient: Okay, doctor. What did the tests show?

Doctor: The biopsy confirms that you have nasopharyngeal carcinoma. This is a type of cancer that starts in the nasopharynx, which is the upper part of your throat behind the nose.

Patient: I see. What caused this cancer?

Doctor: The exact cause isn’t always clear, but we know certain factors increase the risk, like infection with the Epstein-Barr virus, genetics, and environmental exposures. It’s important to remember that this is not your fault.

Patient: What symptoms should I expect? And what tests will I need next?

Doctor: Symptoms can include nasal congestion, nosebleeds, hearing changes, or lumps in the neck. For staging and treatment planning, we’ll do some imaging scans like MRI or PET-CT, and blood tests. These will help us understand how far the cancer has spread.

Patient: How do I prepare for these tests?

Doctor: Most scans don’t require much preparation, but for some, like PET-CT, you may need to fast for a few hours. We will give you detailed instructions before each test.

Patient: What treatment options are available?

Doctor: Treatment usually involves radiation therapy, sometimes combined with chemotherapy. The approach depends on the stage of the cancer. Our goal is to cure the cancer or control it effectively.

Patient: What are the side effects?

Doctor: Side effects can include fatigue, sore throat, dry mouth, and difficulty swallowing, but we have ways to manage these symptoms. We will support you throughout treatment.

Patient: Is there a chance the cancer will come back?

Doctor: There is always a risk of recurrence, but with proper treatment and follow-up, many patients do very well. We will monitor you closely after treatment.

Patient: Are there any clinical trials I could join?

Doctor: Yes, there are ongoing clinical trials exploring new treatments. I can check if you qualify for any and provide more information.

Patient: Thank you, doctor. I appreciate your help.

Doctor: You’re welcome. We’ll take this one step at a time, and I’m here to support you throughout your treatment.

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## **Testicular cancer**

## Cancer can start any place in the body. Testicular cancer starts in the testicles, which make hormones and sperm in men. It starts when cells in the testicles grow out of control and crowd out normal cells. This makes it hard for the body to work the way it should.

## Cancer cells can spread to other parts of the body. Cancer cells in the testicles can sometimes travel to the lungs and grow there. When cancer cells do this, it’s called metastasis . To doctors, the cancer cells in the new place look just like the ones from the testicles.

## Cancer is always named for the place where it starts. So when testicular cancer spreads to the lung (or any other place), it’s still called testicular cancer. It’s not called lung cancer unless it starts from cells in the lung.

## Nonseminomatous Germ Cell Tumors

NSGCT are very variable in appearance and prognosis. There are four main types of NSGCT that can appear alone, but most often appear as a “mixed” NSGCT, with more than one type present:

* Embryonal carcinoma: present in about 40 percent of tumors and among the most rapidly growing and potentially aggressive tumor types. Embryonal carcinoma can secrete HCG or **alpha fetoprotein (AFP)**.
* Yolk sac carcinoma: the most common type of tumor in children; responds well to chemotherapy in children and adults. Yolk sac tumors almost always secrete AFP.
* Choriocarcinoma: very rare and very aggressive form of testis cancer. Can secrete HCG.
* Teratoma: most often appear as a mixed NSGCT; usually grow locally but can appear in retroperitoneal lymph nodes. Teratoma is chemotherapy- and radiation-resistant and best treated with surgical removal.

## **SYMPTOMS**

Signs and symptoms of testicular cancer include:

* A lump or swelling in either testicle
* A feeling of heaviness in the scrotum
* A dull ache in the lower belly or groin
* Sudden swelling in the scrotum
* Pain or discomfort in a testicle or the scrotum
* Enlargement or tenderness of the breast tissue
* Back pain

Usually testicular cancer only happens in one testicle.

### **When to see a doctor**

See your health care provider if you detect any symptoms that last longer than two weeks. These include pain, swelling or lumps in your testicles or groin area.

**Causes**

It's not clear what causes most testicular cancers.

Testicular cancer starts when something causes changes to the DNA of testicle cells. A cell's DNA holds the instructions that tell the cell what to do. The changes tell the cells to grow and multiply quickly. The cancer cells go on living when healthy cells would die as part of their natural life cycle. This causes a lot of extra cells in the testicle that can form a mass called a tumor.

In time, the tumor can grow beyond the testicle. Some cells might break away and spread to other parts of the body. Testicular cancer most often spreads to the lymph nodes, liver and lungs. When testicular cancer spreads, it's called metastatic testicular cancer.

Nearly all testicular cancers begin in the germ cells. The germ cells in the testicle make sperm. It's not clear what causes DNA changes in the germ cells.

**Risk factors**

Factors that may increase your risk of testicular cancer include:

* **Having an undescended testicle, which is called cryptorchidism.** The testes form in the belly during fetal development. They typically descend into the scrotum before birth. If you have a testicle that never descended, your risk of testicular cancer is higher. The risk is increased even if you've had surgery to move the testicle to the scrotum.
* **Having a family history of testicular cancer.** If testicular cancer runs in your family, you might have an increased risk.
* **Being a young adult.** Testicular cancer can happen at any age. But it's most common in teens and young adults between 15 and 45.
* **Being white.** Testicular cancer is most common in white people.

**DIAGNOSIS**

Testicular cancer is most often found because of the symptoms it causes. Symptoms can be:

* A lump or swelling in the testicle is the most common symptom
* Heaviness or aching in the lower belly or testicles
* Voice changes and facial and body hair growth in a very young boy (early puberty)

If you have signs of testicular cancer the doctor will ask you about your health and examine you. If signs are pointing to testicular cancer, more tests will be done. Here are some of the tests you may need:

Ultrasound: Sound waves are used to make pictures of the inside of your body. This is often the first test done. It helps show if a lump in the testicles is solid or fluid filled. If it’s solid, it's more likely to cause cancer.

Blood tests: Testicular cancer cells often make certain proteins that show up in the blood. Checking for them helps your doctor know which kind of testicular cancer you might have.

Chest x-ray: X-rays may be done to see if the cancer has spread to your lungs.

CT or CAT scan: Uses x-rays to make detailed pictures of your insides. This can show if the cancer has spread.

MRI scan: Uses radio waves and strong magnets instead of x-rays to make detailed pictures. This test may be used to see if the cancer has spread.

PET scan: Uses a special kind of sugar that can be seen inside your body with a special camera. If there’s cancer, this sugar shows up as “hot spots” where the cancer is found. This test can help show if the cancer has spread.

#### **Biopsy**

In a biopsy, the doctor takes out a small piece of tissue to check it for cancer cells. A biopsy is the only way to tell for sure if you have cancer. For many other kinds of cancer, a biopsy is done before surgery. But for testicular cancer, this could spread the cancer, so the biopsy is done during surgery to take out the cancer.

Grading testicular cancer

The cancer cells in the biopsy sample will be graded. This helps doctors predict how fast the cancer is likely to grow and spread. Cancer cells are graded based on how much they look like normal cells. Grades 1, 2, and 3 are used. Cells that look very different from normal cells are given a higher grade (3) and tend to grow faster. Ask the doctor to explain your cancer's grade. The grade helps the doctor decide which treatment is best for you.

## **Treatment**

There are many ways to treat testicular cancer. Surgery, radiation, chemotherapy, and high dose chemotherapy with stem cell transplant are the main types of treatment.

The treatment plan that’s best for you will depend on:

* The stage and grade of the cancer
* The chance that a type of treatment will cure the cancer or help in some way
* Your age
* Other health problems you have
* Your feelings about the treatment and the side effects that come with it

#### **Surgery for testicular cancer**

Surgery to take out the testicle is often the first treatment for testicular cancer. It’s used even when the cancer has spread. Nearby lymph nodes may also be taken out to see if there are cancer cells in them. There are many ways to do this surgery. Talk to your doctor about what will be done and what you can expect

Side effects of surgery

Any type of surgery can have risks and side effects. Be sure to ask the doctor what you can expect. If you have problems, let your doctors know. Doctors who treat testicular cancer should be able to help you with any problems that come up.

#### **Chemo**

Chemo is the short word for chemotherapy – the use of drugs to fight cancer. The drugs are given into a vein. These drugs go into your blood and spread through your body. They kill cells that are fast growing, cancer cells and good cells, like blood cells and hair. Chemo is given in cycles or rounds. Each round of treatment is followed by a break. Chemo cycles last about 3 to 4 weeks. Using 2 or more chemo drugs together often works better than using one drug alone. Treatment lasts for many months.

**Side effects of chemo**

Chemo can make you feel very tired, sick to your stomach, and cause your hair to fall out. But these problems go away after treatment ends.

There are ways to treat most chemo side effects. If you have side effects, be sure to talk to your cancer care team so they can help.

#### **Radiation treatments**

Radiation uses high-energy rays (like x-rays) to kill cancer cells. In testicular cancer, radiation is mainly used to kill cancer cells that have spread to lymph nodes. It can also be used to treat cancer that has spread to the brain or spinal cord.

For testicular cancer, a machine aims a beam of radiation at the testicle. This is called external beam radiation. A cover is put over the healthy testicle to help keep the radiation from harming it.

**Side effects of radiation treatments**

If your doctor suggests radiation treatment, talk about what side effects might happen. The most common side effects of radiation are:

* Skin changes where the radiation is given
* Feeling very tired (fatigue)

Most side effects get better after treatment ends. Some might last longer. Talk to your cancer care team about what you can expect.

#### **High dose chemo and stem cell transplant**

A stem cell transplant lets doctors use higher doses of chemo. In this treatment, a special machine takes the cells that make blood (called stem cells) out of the blood. Then very strong chemo is given. The stem cells are given back to the person after chemo. This is called a transplant, but it’s not surgery – the cells are put back into the blood through a vein.

Transplant is mostly used for testicular cancer that has come back (recurred) after regular chemo. It’s a very complex treatment with a lot of side effects. Ask your doctor if you will get this treatment and what to expect.

#### **What about other treatments I hear about?**

When you have cancer you might hear about other ways to treat the cancer or treat your symptoms. These may not always be standard medical treatments. These treatments may be vitamins, herbs, special diets, and other things. You may wonder about these treatments.

Some of these are known to help, but many have not been tested. Some have been shown not to help. A few have even been found to be harmful. Talk to your doctor about anything you’re thinking about using, whether it’s a vitamin, a diet, or anything else.

### **Determining the type of cancer**

Tests on your cancer cells give your health care team information about the type of testicular cancer that you have. Your care team considers your cancer type when deciding on your treatment.

The most common types of testicular cancer include:

* **Seminoma.** Seminoma testicular cancers tend to happen at an older age. Seminomas often grow and spread more slowly than nonseminomas.
* **Nonseminoma.** Nonseminoma testicular cancers tend to happen earlier in life. They grow and spread quickly. Several types of nonseminomas exist. They include choriocarcinoma, embryonal carcinoma, teratoma and yolk sac tumor.

Other types of testicular cancer exist, but they are very rare.

### **Staging the cancer**

Once your doctor confirms your diagnosis, the next step is to see whether the cancer has spread beyond the testicle. This is called the cancer's stage. It helps your health care team understand your prognosis and how likely your cancer is to be cured.

Tests for staging testicular cancer include:

* **Computerized tomography (CT) scan.** CT scans take a series of X-ray pictures of your belly, chest and pelvis. A health care provider checks the pictures for signs that cancer has spread.
* **Blood tests.** Tumor marker tests are often repeated after surgery to remove the testicle. The results help your health care provider decide whether you might need additional treatments to kill the cancer cells. Tumor marker tests might be used during and after cancer treatment to monitor your condition.

The stages of testicular cancer range from 0 to 3. In general, stage 0 and stage 1 cancers only affect the testicle and the area around it. At these early stages, the cancer hasn't spread to the lymph nodes or other parts of the body. Stage 2 testicular cancers have spread to the lymph nodes. When testicular cancer spreads to other parts of the body, it is stage 3. Not all stage 3 cancers have spread though. Stage 3 can also mean that the cancer is in the lymph nodes and the tumor marker results are very high.

**Prevention**

There's no way to prevent testicular cancer. If you get testicular cancer, there's nothing you could have done to prevent it.

### **Testicular cancer screening**

Some health care providers recommend regular testicle self-exams. During a testicular self-exam you feel your testicles for any lumps or other changes.

Not all health care providers agree with this recommendation. There's no research to show that self-exams can lower the risk of dying of testicular cancer. Even when it is found at a late stage, testicular cancer is likely to be cured.

Still, you might find it helpful to become aware of the usual feel of your testicles. You can do this by doing a testicular self-exam. If you notice any changes that last longer than two weeks, make an appointment with your healthcare provider.

**DIFFERENTIAL DIAGNOSIS**

A hard intratesticular mass is a diagnostic of testicular cancer unless proven otherwise. However, some other diagnoses to consider while evaluating a testicular mass include:

* Epididymo-orchitis
* Hematoma
* Inguinal hernia
* Hydrocele
* Spermatocele or epididymal head cyst
* Varicocele
* Lymphoma (the most common finding in bilateral testis lesions in older men)
* Metastasis from other cancers (eg, lung cancer, melanoma, prostate cancer)
* Syphilitic gumma
* Tuberculoma

Ultrasonography helps further narrow down the diagnosis and radical inguinal orchiectomy is the definitive modality for diagnosis.

**genes related to the pathogenesis and their respective chromosomes as outlined below:**

* UCK1: Chromosome 1
* HPGDS: Chromosome 4
* CENPE: Chromosome 4
* TERT: Chromosome 5
* TERT/CLPTM1L: Chromosome 5
* SPRY4: Chromosome 5
* BAK-1: Chromosome 6
* MAD1L1: Chromosome 7
* DMRT1: Chromosome 9
* AFT7IP: Chromosome 12
* KITLG: Chromosome 12
* RFWD3: Chromosome 16
* TEX14: Chromosome 17
* PPM1E: Chromosome 17

**EPIDEMIOLOGY**

The highest incidence of testicular cancer is observed in Western and Northern Europe (8.7 and 7.2 per 100,000 men, respectively). The highest mortality rates are reported in western Asia, with most countries showing a decrease in mortality, likely due to the combined impact of earlier detection through self-examination and integration of multimodal treatments.

In the United States, testicular cancer is most frequently diagnosed among men aged 20 to 34 (51% of all cases). 22.9 % of the cases are diagnosed in the age group of 35 to 44, 12.9% between 45 to 54, and the rest in other age groups. The mean age of diagnosis is 33 years. It is more commonly seen in White race men with an incidence rate of 7.1 per 100,000 persons, compared to 5.4 in Hispanic men and 1.7 in African American men.

The overall incidence in the United States increased gradually over the last 4 decades (6.3 per 100,000 persons in 2017 compared to 3.7 per 100,000 in 1975). Testicular cancer incidence is higher in industrialized countries than in developing countries and, while higher incidences are seen in Caucasian men, the incidence of testicular cancer among non-white and immigrant men within the United States is increasing for unknown reasons.Synchronous contralateral tumors are seen in 0.6% of cases and metachronous contralateral tumors are identified in 1.9% of cases

### **QUESTION AND ANSWER SET**

### **What is the most aggressive form of testicular cancer?**

Two of the most aggressive forms of testicular cancer are choriocarcinomas, which are rare, and embryonal carcinomas, which are much more common.

### **What is the least aggressive testicular cancer?**

Spermatocytic tumors, which tend to develop in older males, are among the least aggressive testicular cancers. These tumors tend not to spread

beyond the testicles.

But because these tumors are less aggressive, diagnosis often occurs after the tumors have been growing for a long time.

### **Which is worse — seminoma or nonseminoma?**

Both seminomas and nonseminomas are treatable cancers, especially if diagnosed early. But nonseminomas are more aggressive and tend to affect males at a younger age compared with seminomas.

## **Doctor-Patient Conversation: Testicular Cancer**

Doctor: Hello, thanks for coming in today. I have reviewed your ultrasound and blood test results, and I’d like to discuss what we found.

Patient: Okay, doctor. What did the tests show?

Doctor: The ultrasound showed a solid mass in your testicle, and the blood tests revealed elevated tumor markers. These findings suggest that you have testicular cancer.

Patient: I see. What exactly is testicular cancer?

Doctor: Testicular cancer is a type of cancer that starts in the testicles, which are the male reproductive glands. It’s relatively rare but one of the most treatable cancers, especially when caught early.

Patient: What caused it? Did I do something wrong?

Doctor: The exact cause isn’t always clear. Some risk factors include a history of undescended testicle, family history, or certain genetic factors. But it’s important to know that it’s nobody’s fault.

Patient: What happens next? How do we treat it?

Doctor: The next step is usually surgery to remove the affected testicle, called a radical inguinal orchiectomy. This also helps us confirm the diagnosis and stage the cancer. Depending on the type and stage, you may need additional treatments like chemotherapy or radiation.

Patient: Will I still be able to have children?

Doctor: Many men can still father children after treatment, especially if only one testicle is removed. We can discuss sperm banking before treatment if you’re concerned.

Patient: What about side effects or risks from treatment?

Doctor: Surgery is generally safe, but there are risks like any operation. Chemotherapy or radiation can have side effects such as fatigue, nausea, or risk to fertility, but we will manage these carefully.

Patient: Is this cancer likely to come back?

Doctor: With early treatment, the cure rate is very high. We will monitor you regularly after treatment to catch any recurrence early.

Patient: Are there support resources or clinical trials I can consider?

Doctor: Yes, I can connect you with support groups and provide information about clinical trials if you’re interested.

Patient: Thank you, doctor. This is a lot to take in, but I appreciate your help.

Doctor: I understand this is overwhelming. Take your time, and feel free to ask any questions. We’re here to support you every step of the way.

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**OSTEOSARCOMA**

**DEFINITION AND DESCRIPTION**

Osteosarcoma is a kind of cancer that begins in the cells that form bones. Osteosarcoma tends to happen most often in teenagers and young adults. But it also can happen in younger children and older adults.

Osteosarcoma can start in any bone. It's most often found in the long bones of the legs, and sometimes the arms. Very rarely, it happens in soft tissue outside the bone.

Advances in the treatment of osteosarcoma have improved the outlook for this cancer. After treatment for osteosarcoma, people sometimes face late effects from the strong treatments used to control the cancer. Healthcare professionals often suggest lifelong monitoring for side effects after treatment.

**Causes**

It's not clear what causes osteosarcoma.

Osteosarcoma happens when bone cells develop changes in their DNA. A cell's DNA holds the instructions, called genes, that tell a cell what to do. In healthy cells, the DNA gives instructions to grow and multiply at a set rate. The instructions tell the cells to die at a set time.

In cancer cells, the DNA changes give different instructions. The changes tell the cancer cells to make many more cells quickly. Cancer cells can keep living when healthy cells die. This causes too many cells.

The cancer cells might form a mass called a tumor. The tumor can grow to invade and destroy healthy body tissue. In time, cancer cells can break away and spread to other parts of the body. When cancer spreads, it's called metastatic cancer.

**Risk factors**

Most people with osteosarcoma don't have any known risk factors for cancer. But these factors can increase the risk of osteosarcoma:

* Certain conditions that run in families. These include hereditary retinoblastoma, Bloom syndrome, Li-Fraumeni syndrome, Rothmund-Thomson syndrome and Werner syndrome.
* Other bone conditions. These include Paget's disease of bone and fibrous dysplasia.
* Prior treatment with radiation therapy or chemotherapy.

There is no way to prevent osteosarcoma.

**Complications**

Complications of osteosarcoma and its treatment include the following.

### **Cancer that spreads, also called metastasizes**

Osteosarcoma can spread from where it started to other areas. This makes treatment and recovery harder. Osteosarcoma most often spreads to the lungs, the same bone or another bone.

### **Coping after surgery to remove an arm or leg**

Surgeons aim to remove the cancer and spare the arm or leg when they can. But sometimes surgeons need to remove part of the affected limb to remove all the cancer. Learning to use an artificial limb, called a prosthesis, takes time, practice and patience. Experts can help.

### **Long-term treatment side effects**

The strong treatments needed to control osteosarcoma can cause major side effects, both in the short and long term. Your healthcare team can help you or your child manage the side effects that happen during treatment. The team also can give you a list of side effects to watch for in the years after treatment.

**Symptoms**

Osteosarcoma signs and symptoms most often start in a bone. The cancer most often affects the long bones of the legs, and sometimes the arms. The most common symptoms include:

* Bone or joint pain. Pain might come and go at first. It can be mistaken for growing pains.
* Pain related to a bone that breaks for no clear reason.
* Swelling near a bone.

### **When to see a doctor**

Make an appointment with a healthcare professional if you or your child has ongoing symptoms that worry you. Osteosarcoma symptoms are like those of many more common conditions, such as sports injuries. The health professional might check for those causes first.

## **Diagnosis**

Osteosarcoma diagnosis may begin with a physical exam. Based on the findings of the exam, there might be other tests and procedures.

### **Imaging tests**

Imaging tests make pictures of the body. They can show the location and size of an osteosarcoma. Tests might include:

* X-ray.
* MRI.
* CT.
* Bone scan.
* Positron emission tomography scan, also called a PET scan.

### **Removing a sample of cells for testing, called a biopsy**

A biopsy is a procedure to remove a sample of tissue for testing in a lab. The tissue might be removed using a needle that is put through the skin and into the cancer. Sometimes surgery is needed to get the tissue sample. The sample is tested in a lab to see if it is cancer. Other special tests give more details about the cancer cells. Your healthcare team uses this information to make a treatment plan.

Determining the type of biopsy needed and how it should be done requires careful planning by the medical team. The biopsy needs to be done so that it won't get in the way of future surgery to remove the cancer. Before having a biopsy, ask your healthcare professional to refer you to a team of experts who have experience treating osteosarcoma.

**Treatment**

Osteosarcoma treatment most often involves surgery and chemotherapy. Rarely, radiation therapy also might be an option if the cancer can't be treated with surgery.

### **Surgery**

The goal of surgery is to remove all the cancer cells. In planning the surgery, the healthcare team keeps in mind how the surgery will affect your or your child's daily life. The extent of surgery for osteosarcoma depends on several factors, such as the size of the cancer and where it is.

Operations used to treat osteosarcoma include:

* **Surgery to remove the cancer only, also called limb-sparing surgery.** Most osteosarcoma operations can be done in a way that removes all the cancer and spares the arm or leg. Whether this type of surgery is an option depends, in part, on the extent of the cancer and how much muscle and tissue need to be removed.  
  If a section of bone is removed, the surgeon will rebuild the bone. How the bone is rebuilt depends on the situation. Options include metal implants or bone grafts.
* **Surgery to remove the affected arm or leg, also called amputation.** Rarely a surgeon might remove the affected leg or arm to get all the cancer. After surgery, an artificial arm or leg can be used. This is called a prosthesis.
* **Surgery to remove the lower portion of the leg, also called rotationplasty.** Rotationplasty might be an option for osteosarcoma in and around the knee joint. In this surgery, the surgeon removes the cancer and surrounding area, including the knee joint. The foot and ankle are then rotated and put backward on the part of the leg that remains above the knee. The ankle then works as a knee.  
  A prosthesis is used for the lower leg and foot. This surgery is sometimes a good option for children who are still growing. It allows them to take part in sports and physical activities.

### **Chemotherapy**

Chemotherapy treats cancer with strong medicines.

For osteosarcoma, chemotherapy often is used before surgery. It can shrink the cancer and make it easier to remove.

After surgery, chemotherapy treatments might be used to kill any cancer cells that might remain.

For osteosarcoma that returns after surgery or spreads to other areas of the body, chemotherapy might help relieve pain and slow the growth of the cancer.

### **Radiation therapy**

Radiation therapy treats cancer with powerful energy beams. The energy can come from X-rays, protons or other sources. During radiation therapy, you lie on a table while a machine moves around your body. The machine directs radiation to precise points on your body.

Radiation is not often used to treat osteosarcoma. Radiation therapy might be suggested instead of surgery if surgery can't remove all the cancer.

.**staging system**

Another system sometimes used to stage bone cancers (including osteosarcomas) This system is based on 4 key pieces of information:

* T describes the size of the main (primary) tumor and if it appears in different areas of the bone.
* N describes the extent of spread to nearby (regional) lymph nodes. Bone tumors rarely spread to the lymph nodes.
* M indicates if the cancer has metastasized (spread) to other organs of the body. (The most common sites of spread are to the lungs or other bones.)
* G stands for the grade of the tumor, which describes how the cells look under a microscope. Low-grade tumor cells look more like normal cells and are less likely to grow and spread quickly, while high-grade tumor cells look more abnormal.

Numbers after T, N, M, and G give more details about each of these factors.

Once the T, N, and M categories and the grade of the bone cancer have been determined, the information is combined into an overall stage. These stages (which are different from those of the MSTS system) are described using Roman numerals from I to IV (1 to 4), and are sometimes divided further.

## **QUESTION AND ANSWERS SET**

## What type of cancer is this?

Osteosarcoma is a primary malignant bone tumor that usually arises in the long bones near the growth plates, such as the thigh bone or shin bone. It is a high-grade sarcoma characterized by the production of immature bone or osteoid by malignant cells.

## Has the cancer spread?

* Osteosarcoma can be localized (confined to the bone and nearby tissues) or metastatic (spread to other parts of the body).
* About 80% of cases are localized at diagnosis, while roughly 20% have spread, most commonly to the lungs, but also to other bones or organs.
* Staging systems classify spread as:
  + Stage I and II: localized disease (low or high grade).
  + Stage III: multiple tumors in the same bone.
  + Stage IV: metastases to lungs or other sites.

## Are more tests needed?

Yes. After diagnosis by biopsy, further tests include:

* Imaging scans such as MRI of the affected bone to assess local extent.
* CT scans of the chest to check for lung metastases.
* Possible bone scans or PET scans to detect spread to other bones or organs.
* Blood tests and biopsy results help determine tumor grade and stage.

## What are the treatment options?

* Surgery to remove the tumor, often limb-sparing surgery if possible.
* Chemotherapy before and after surgery to treat microscopic spread and reduce recurrence risk.
* Radiation therapy is less commonly used but may be considered in some cases.

## What are the chances that treatment will cure this cancer?

* For localized osteosarcoma, the cure rate is approximately 60-80% with combined surgery and chemotherapy.
* If the cancer has spread (metastatic), cure rates are lower but some patients can still be cured, especially if metastases can be surgically removed and chemotherapy is effective.

## What are the side effects and risks of each treatment option?

* Surgery risks: infection, bleeding, nerve or blood vessel damage, possible need for amputation if limb-sparing is not feasible.
* Chemotherapy side effects: nausea, vomiting, hair loss, fatigue, risk of infection, kidney or heart damage (depending on drugs used).
* Radiation therapy (if used): skin irritation, fatigue, risk of damage to nearby tissues.

## Which treatment do you think is best?

* The standard and most effective treatment is neoadjuvant chemotherapy (before surgery), followed by surgical removal of the tumor, then adjuvant chemotherapy (after surgery).
* The exact plan depends on tumor size, location, spread, and patient health.
* Your oncology team will tailor the treatment to maximize cure chances and preserve function.

## Will treatment affect being able to have children? If so, do you offer ways to preserve that ability?

* Chemotherapy can affect fertility in both males and females.
* Before starting treatment, fertility preservation options such as sperm banking (for males) or egg/embryo freezing (for females) should be discussed.
* Your care team can refer you to fertility specialists to explore these options

**DIFFERENTIAL DIAGNOSIS**

Benign Conditions

Osteomyelitis (bone infection): Can cause bone destruction and periosteal reaction similar to osteosarcoma.

Aneurysmal bone cyst: Benign expansile cystic lesion that may mimic telangiectatic osteosarcoma radiologically.

Osteoblastoma: Benign bone tumor that can resemble low-grade osteosarcoma histologically.

Giant cell tumor of bone: Usually occurs in epiphysis, but can be confused with osteosarcoma in some cases.

Fibrous dysplasia: Benign fibro-osseous lesion with bone expansion and irregular bone formation.

Malignant Conditions

Ewing sarcoma: Another primary malignant bone tumor, typically located in diaphyseal region, often in younger patients; distinguished by different radiologic and histologic features.

Malignant fibrous histiocytoma (undifferentiated pleomorphic sarcoma): Can mimic osteosarcoma, especially osteolytic variants.

Fibrosarcoma of bone: Rare malignant tumor that may resemble osteosarcoma histologically.

Lymphoma of bone: May mimic osteosarcoma on imaging.

**EPIDEMIOLOGY**

Metastatic bone tumors: Secondary tumors from other primary cancers, though less common in young patients.

The incidence of osteosarcoma is about 3.4 cases per million people per year.Osteosarcomas constitute <1% of all newly diagnosed malignancies in adults and nearly 4% of all newly diagnosed malignancies in children.Excluding hematological malignancies, osteosarcoma is the most commonly diagnosed malignancy in adolescents, with an incidence of 4.4 per million per year. Osteosarcoma does have a slightly increased incidence in males versus females Approximately 20% of osteosarcoma are metastatic at presentation. Between 60% and 70% of metastatic disease is to the lungs; another 20% to 30% of metastatic lesions are skip or distant bony metastases.

Primary osteosarcoma is primarily a lesion of childhood and adolescence with a marked propensity for the knee. Secondary osteosarcoma reflects the varied nature of the predisposing condition with a broader age distribution, primarily within adulthood. Secondary osteosarcoma is much more likely to occur in flat bones, including the pelvis; this is likely due to the causative effect of Paget's disease of bone, which shares a similar anatomical preference

**RECOMMENDATION GUIDELINE**

management guidelines based on the grade and resectability of a tumor:

* Low-grade osteosarcoma without metastasis
  + Intramedullary and surface
    - Wide excision alone (ie, no neoadjuvant chemotherapy)
      * If post surgical pathology demonstrates low-grade features, then adjuvant chemotherapy is not recommended.
      * If post surgical pathology demonstrates high-grade features, consider adjuvant chemotherapy.
  + Periosteal
    - Consider neoadjuvant chemotherapy
    - Wide excision
      * If postsurgical pathology demonstrates is consistent with biopsy (low-grade features only), no adjuvant chemotherapy is recommended.
      * If postsurgical pathology demonstrates high-grade features, adjuvant chemotherapy is recommended.
* High-grade intramedullary or surface osteosarcoma without metastasis
  + Neoadjuvant chemotherapy; then restage the lesion
    - If restaging suggests the lesion is resectable, perform a limb-sparing wide excision.
      * Positive margins
        + If a favorable response to preoperative neoadjuvant chemotherapy (<10% viable tumor on postsurgical pathology) was seen, then continue the same neoadjuvant chemotherapy regimen and consider additional surgical resection with or without radiation therapy.
        + If an inadequate response to preoperative neoadjuvant chemotherapy (eg, >10% viable tumor on postsurgical pathology) is noted, then continue the same neoadjuvant chemotherapy regimen or consider a new regimen and consider additional surgical resection with or without radiation therapy.
      * Negative margins
        + If a good response to preoperative neoadjuvant chemotherapy (ie, <10% viable tumor on postsurgical pathology) was observed, continue the same neoadjuvant chemotherapy regimen. No further resection is required.
        + If an inadequate response to preoperative neoadjuvant chemotherapy (ie, ≥10% viable tumor on postsurgical pathology) is noted, continue the same neoadjuvant chemotherapy regimen or consider a new regimen. No further resection is required.
  + If restaging suggests the lesion is unresectable, then continue chemotherapy and consider radiation therapy.
* Any grade with metastasis at presentation, follow guidelines for high-grade osteosarcoma plus the following:
  + If metastases are resectable (eg, pulmonary, visceral, or skeletal sites), a metastasectomy should be performed (see **Image.** Pulmonary Metastasis of Osteogenic Sarcoma).
  + If metastases are unresectable, then consider chemotherapy and radiation therapy, after which the primary site requires reassessment for local control.
* Follow-up and surveillance
  + Surveillance schedule
    - Every 3 months for postoperative years 1 and 2
    - Every 4 months in postoperative year 3
    - Every 6 months in postoperative years 4 and 5
    - Yearly for postoperative years 6 and beyond
  + Surveillance visits should include:
    - Physical exam with assessment of function
    - Contrast-enhanced CT with or without MRI of the postoperative site and chest
  + Consider PET/CT or bone scan
  + Complete blood count with additional laboratory tests as clinically indicated (eg, alkaline phosphatase levels)
  + If a relapse is detected, chemotherapy with resection, if possible, should be resumed in conjunction with the following guidelines:
    - Evaluate tumor treatment by performing radiographs of the original tumor site, CT or MRI with contrast of the site of relapse, and CT of the chest to assess for pulmonary lesions
    - In tumors responsive to treatment (ie, <10% viable tumor on postsurgical pathology), continue surveillance (ie, restart OSTEO-4 guidelines)
    - In tumors with a poor response to treatment (ie, ≥10% viable tumor on postsurgical pathology) or continued progression of the disease, management strategies include:
      * Resection (if possible)
      * Clinical trial
      * Palliative radiation
      * Best supportive care

**Recurrent Osteogenic Sarcoma**

In individuals with recurrent disease with or without metastasis, surgical resection is preferred if possible; primarily, adjuvant chemotherapy is given. A 5-year survival rate of 33% may be obtained in patients with a second surgical remission.. In patients who are not candidates for surgery, chemotherapy with or without radiation is preferred. In those with metastasis, dismal 5-year survival rates of 20%, which has remained unchanged over the past 25 years, underline the need to explore newer approaches.

**Supportive Management and Palliative Medicine**

The management of chemotherapy-related complications such as nausea and vomiting, anemia, neutropenic fever, fatigue, neuropathy, and cardiotoxicity, provision of symptom-directed therapy, and counseling regarding goals of care discussions have shown improvement in the quality of life. The provision of continuity of care through home care and round-the-clock telephonic liaison might assume special significance, depending on environmental circumstances (eg, the COVID-19 pandemic). Hospice should be considered early.

## **Doctor-Patient Conversation: Osteosarcoma**

Doctor: Hello, thank you for coming in today. I have reviewed your biopsy and imaging results, and I’d like to discuss what we found.

Patient: Okay, doctor. What did the tests show?

Doctor: The biopsy confirms that you have osteosarcoma, which is a type of bone cancer. It usually starts in the long bones, like your thigh or shin bone, and it’s important we begin treatment promptly.

Patient: I see. What causes this cancer?

Doctor: The exact cause is not always clear. Sometimes it’s related to rapid bone growth during adolescence, previous radiation exposure, or certain genetic factors. But often, it occurs without a known cause.

Patient: Has the cancer spread?

Doctor: We have done scans of your chest and bones. So far, it appears localized to the bone where the tumor started, which is good news. We will continue careful monitoring throughout treatment.

Patient: What treatment will I need?

Doctor: Treatment usually involves chemotherapy before and after surgery to remove the tumor. We aim to save the limb if possible, but sometimes more extensive surgery is needed. Chemotherapy helps kill any cancer cells that might have spread microscopically.

Patient: What are the chances of curing this?

Doctor: For localized osteosarcoma, the cure rate is about 60 to 80 percent with combined chemotherapy and surgery. We will do everything we can to give you the best outcome.

Patient: What side effects should I expect?

Doctor: Chemotherapy can cause nausea, hair loss, fatigue, and increased risk of infection. Surgery risks depend on the extent of the operation but can include pain and changes in limb function. We will support you through all of these.

Patient: Will this affect my ability to have children?

Doctor: Chemotherapy can affect fertility. Before starting treatment, we can discuss options like sperm banking or other fertility preservation methods to help protect your ability to have children in the future.

Patient: Are there any other tests I need?

Doctor: We’ve done the main staging scans, but we will monitor you closely with regular imaging and blood tests during and after treatment.

Patient: Thank you, doctor. This is a lot to take in, but I appreciate your help.

Doctor: I understand it’s overwhelming. Please feel free to ask any questions anytime. We’re here to support you every step of the way.

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**LIPOSARCOMA**

**DEFINITION AND DESCRIPTION**

Liposarcoma is a rare type of cancer that starts in the fat cells. It most often begins as a growth of cells in the belly or in the arm and leg muscles. But liposarcoma can begin in the fat cells anywhere in the body.

Liposarcoma happens most often in older adults, but it can happen at any age.

Liposarcoma treatment usually involves surgery to remove the cancer. Other treatments, such as radiation therapy, also may be used.

Liposarcoma is a type of cancer called a soft tissue sarcoma. These cancers happen in the body's connective tissues. There are many types of soft tissue sarcoma.

**Symptoms**

Liposarcoma symptoms depend on the part of the body where the cancer forms.

Liposarcoma in the arms and legs can cause:

* A growing lump of tissue under the skin.
* Pain.
* Swelling.
* Weakness of the affected limb.

Liposarcoma in the belly, also called the abdomen, can cause:

* Abdominal pain.
* Abdominal swelling.
* Feeling full sooner when eating.
* Constipation.
* Blood in stool.

### **When to see a doctor**

Make an appointment with a doctor or other health care professional if you have any symptoms that don't go away and that worry you.

**Causes**

It's not clear what causes liposarcoma.

Liposarcoma starts when fat cells get changes in their DNA. A cell's DNA holds the instructions that tell the cell what to do. The changes turn the fat cells into cancer cells. The changes tell the cancer cells to grow quickly and make a lot of extra cells. The cancer cells keep living when healthy cells would die as part of their natural life cycle.

The cancer cells form a growth, called a tumor. In some types of liposarcoma, the cancer cells stay put. They continue making more cells, causing the tumor to get bigger. In other types of liposarcoma, the cancer cells might break away and spread to other parts of the body. When cancer spreads to other parts of the body, it's called metastatic cancer.

## **Diagnosis**

Tests and procedures used to diagnose liposarcoma include:

* **Imaging tests.** Imaging tests create pictures of the inside of the body. They might help show the size of the liposarcoma. Tests may include X-ray, CT scan and MRI. Sometimes a positron emission tomography scan, also called a PET scan, is needed.
* **Removing a sample of tissue for testing.** A procedure to remove some cells for testing is called a biopsy. The sample might be removed with a needle put through the skin. Or the sample might be taken during surgery to remove the cancer. The type of biopsy depends on the cancer's location.
* **Testing the cancer cells in a lab.** The biopsy sample goes to a lab for testing. Doctors who specialize in analyzing blood and body tissue, called pathologists, test the cells to see if they're cancerous. Other special tests give more details. Your health care team uses the results to understand your prognosis and create a treatment plan.

**Treatment**

Treatments for liposarcoma include:

* **Surgery.** The goal of surgery is to remove all of the cancer cells. Whenever possible, surgeons work to remove the entire liposarcoma without damaging any surrounding organs.  
  If a liposarcoma grows to involve nearby organs, removal of the entire liposarcoma may not be possible. In those situations, your health care team may recommend other treatments to shrink the liposarcoma. That will make it easier to remove during an operation.
* **Radiation therapy.** Radiation therapy uses powerful energy beams to kill cancer cells. The energy can come from X-rays, protons or other sources. Radiation may be used after surgery to kill any cancer cells that remain. Radiation also may be used before surgery to shrink a tumor to make it more likely that surgeons can remove the entire tumor.
* **Chemotherapy.** Chemotherapy uses strong medicines to kill cancer cells. Some chemotherapy medicines are given through a vein and some are taken in pill form. Not all types of liposarcoma are sensitive to chemotherapy. Careful testing of your cancer cells can show whether chemotherapy is likely to help you.  
  Chemotherapy may be used after surgery to kill any cancer cells that remain. It also may be used before surgery to shrink a tumor. Chemotherapy is sometimes combined with radiation therapy.

#### **What are the treatment side effects?**

Side effects include recovering from surgery, as well as side effects from chemotherapy and radiation therapy.

#### **What are treatment complications?**

Healthcare providers typically treat liposarcoma with surgery to remove the tumor and nearby healthy tissue. Any type of surgery may have complications. Your surgeon will discuss your specific situation, but some common surgery complications may include:

* Reaction to general anesthesia.
* Blood loss.
* Surgical wounds that don’t heal.
* Infection.
* Damage to organs or tissues affected by the tumor.
* Pain that isn’t managed by pain medication.

## **Outlook / Prognosis**

That depends on the type of liposarcoma you have and if it’s spread. For example, if you have well-differentiated liposarcoma that hasn’t spread, your surgeon may be able to remove the entire tumor. If the tumor doesn’t come back, your provider may consider you cured.

There are several types of liposarcoma with very different prognoses. If you have this condition, your healthcare provider is your best resource for information.

### **What can I expect if I have this condition?**

Each liposarcoma type is different, so your healthcare provider is your best resource for information about what you may expect, given your situation. In general, you may:

* Need more than one surgery to remove the tumor or to remove a tumor that’s come back.
* Need treatment in addition to or instead of surgery. Many times, surgeons successfully treat some liposarcoma by removing the tumor. But sometimes, surgery isn’t an option, which means you’ll need different treatment that may keep a tumor from spreading or growing but may not eliminate it.
* Need ongoing treatment to keep tumors from spreading.
* Need long-term follow-up. Once you’ve completed treatment, your provider will monitor your overall health and watch for any signs of new tumors. They may recommend regular follow-up appointments for at least 10 years.
* Need emotional support. Cancer can be lonely, particularly if you have a rare cancer. Ask your provider about programs and services to help you deal with the emotional impact of having a rare disease.

## **Prevention**

Unfortunately, you may not be able to prevent liposarcoma, particularly if you have an inherited condition that increases your risk of developing the condition. You can reduce your risk of soft tissue cancers by avoiding long-term exposure to radiation and toxic chemicals such as vinyl chloride.

## **Living With**

Unfortunately, you can’t prevent liposarcoma from coming back. Often, people with cancer that might return feel anxious every time they have a follow-up appointment. (Some cancer specialists call this “scanxiety.”) If you’re feeling anxious about the future, ask your provider what you can expect based on your situation.

## **QUESTION AND ANSWER SET**

## Do I have cancer?

If you have been diagnosed with liposarcoma, yes, this is a type of cancer that arises from fat cells in soft tissues, often in the arms, legs, or retroperitoneum (abdomen). It is a malignant tumor that requires treatment.

## Do I need more tests?

Yes. After initial diagnosis by biopsy, further tests such as MRI or CT scans are needed to determine the tumor’s size, exact location, and whether it has spread (staging). Chest imaging is important to check for lung metastases. Additional blood tests and possibly molecular studies may also be done to guide treatment.

## Can I have a copy of my pathology report?

Absolutely. You have the right to request a copy of your pathology report. It contains important details about the tumor type, grade, and other features that help guide treatment.

## What are my treatment options?

* Surgery is the primary treatment to remove the tumor completely, aiming for clear margins.
* Radiation therapy may be used before surgery to shrink the tumor or after surgery to kill remaining cancer cells.
* Chemotherapy is sometimes used, especially for aggressive or advanced tumors, but not all liposarcoma types respond well.
* Targeted therapies and immunotherapies are emerging options, particularly for advanced or metastatic disease.

## What are the potential risks of each treatment option?

* Surgery risks: Infection, bleeding, damage to surrounding tissues, and functional impairment depending on tumor location.
* Radiation therapy risks: Skin irritation, fatigue, and possible damage to nearby organs.
* Chemotherapy risks: Nausea, hair loss, fatigue, increased infection risk, and organ toxicity depending on drugs used.
* Targeted therapies: Side effects vary by drug but may include fatigue, nausea, and blood count changes.

## Can any treatments cure my cancer?

Yes. Surgery combined with radiation and/or chemotherapy can cure many patients, especially if the tumor is detected early and completely removed. The prognosis depends on tumor subtype, size, location, and whether it has spread. Well-differentiated tumors have better outcomes, while high-grade or metastatic tumors have lower cure rates.

## Is there one treatment you think is best for me?

The best treatment depends on your tumor’s specific features and your overall health. Typically, complete surgical removal is the cornerstone, often combined with radiation and sometimes chemotherapy. Your oncology team will tailor the plan to maximize effectiveness and minimize side effects.

## If you had a friend or family member in my situation, what would you recommend?

I would recommend seeking care at a specialized center with experience in sarcomas, following the recommended treatment plan including surgery and appropriate adjunct therapies, and considering participation in clinical trials if eligible. Supportive care and open communication with your medical team are also important.

## How much time can I take to choose a treatment?

While it’s important to start treatment promptly, you should take some time to understand your diagnosis and options. Discuss with your doctor how soon treatment should begin based on your tumor’s aggressiveness. Usually, a few weeks is reasonable to make an informed decision.

## How will cancer treatment affect my daily life?

Treatment side effects vary but may include fatigue, pain, limited mobility (depending on surgery site), and emotional stress. Radiation and chemotherapy can cause additional symptoms like nausea or skin changes. Your care team will help manage these effects and support your quality of life.

## Should I see a specialist? What will that cost, and will my insurance cover it?

Yes, seeing a sarcoma specialist or multidisciplinary cancer center is strongly recommended for optimal care. Costs and insurance coverage vary by country and plan. Your healthcare provider or insurance company can provide details about coverage and referrals.

## 

## **Diagnostic Considerations**

Also consider the following:

* Cellular angiofibroma
* Solitary fibrous tumor
* Cutaneous neurofibroma
* Malignant schwannoma
* Rhabdomyosarcoma
* Leiomyosarcoma
* Fibrous histiocytoma
* Benign lipoblastoma in infants and children
* Actinomycosis
* Salivary gland tumors

Late granulomatous reactions from silicone may appear in a site different from that of the injection and may cause an incorrect diagnosis of liposarcoma.Silicone implants for chin augmentation may create a tissue reaction that mimics a low-grade liposarcoma.

Myxofibrosarcoma, one of the most common soft tissue sarcomas of elderly patients, may histologically resemble pleomorphic liposarcoma.

Primary liposarcoma may be evident as metastatic liposarcoma to the head and neck region, including the gingival mucosa.

Spindle cell lipomas are benign lipomatous tumors that may require histological distinction from liposarcoma. These lipomas are typically seen in the posterior neck, shoulder, or upper back of older males.

Because cutaneous liposarcoma is extremely rare, the physician must rule out a metastatic lesion.

## **Differential Diagnoses**

* Actinomycosis
* Cutaneous Lipomas
* Dermatologic Manifestations of Neurofibromatosis Type 1

## 

## **Epidemiology**

### Frequency

*United States*

Soft tissue sarcomas occur in approximately 5000 patients in the United States per year. Overall, liposarcomas account for less than 20% of all soft tissue sarcomas, and the average patient age at presentation is 50 years. However, in children, liposarcomas account for less than 5% of all soft tissue sarcomas; fewer than 60 cases in children have been reported.

*International*

With an annual incidence of 2.5 cases per million population, liposarcoma is the most common soft tissue sarcoma, accounting for approximately 17% of all soft tissue sarcomas and 3% of all liposarcomas in the head and neck region (usually the neck and the cheek). Oral involvement is rare; as of the year 2000, fewer than 50 oral cases had been reported. The trunk and the lower extremities are the most likely sites of tumor development.

### Race and sex

No association with race or geography is known.

Liposarcomas are slightly more common in males than in females.

### Age

The mean patient age at onset is 50 years. Although liposarcomas account for about 17% of all soft tissue sarcomas, they are involved in only 4% of childhood soft tissue sarcomas. Cases of liposarcoma are reported in young adults and teenagers, but cases in children are rare.

## **PROCEDURES AND TIMELINE**

## Diagnosis Phase

* Initial evaluation: Physical exam and symptom review.
* Imaging tests: MRI or CT scans to determine tumor size, location, and involvement of nearby structures.
* Biopsy: Core needle or incisional biopsy to confirm diagnosis and subtype.
* Additional staging scans: Chest CT to check for lung metastases; sometimes PET scan or bone scan.
* Timeline: Diagnosis and staging typically take 1 to 3 weeks from first presentation.

## Treatment Phase

## 1. Surgery

* Goal: Complete removal of the tumor with clear margins while preserving function.
* Timing: Usually scheduled within 2 to 6 weeks after diagnosis and staging, depending on patient health and tumor complexity.
* Recovery: Surgical recovery can take weeks to months, especially for large tumors or those near critical structures.

## 2. Radiation Therapy

* Use: May be given before surgery to shrink large tumors or after surgery to reduce recurrence risk.
* Duration: Typically delivered over 5 to 7 weeks with daily sessions (Monday to Friday).
* Side effects: Local skin irritation, fatigue; long-term effects depend on the radiation site.

## 3. Chemotherapy

* Use: Reserved mainly for high-grade, metastatic, or unresectable liposarcomas (e.g., myxoid, pleomorphic, dedifferentiated types).
* Regimens: Anthracycline-based chemotherapy is common; newer agents like trabectedin and eribulin are FDA-approved for advanced disease.
* Duration: Usually given in cycles over several months (e.g., 3 to 6 months).
* Effectiveness: Varies by subtype; well-differentiated liposarcoma is generally resistant.

## 4. Follow-up and Monitoring

* Frequency: Regular imaging and physical exams every 3 to 6 months for the first 2 to 3 years, then less frequently.
* Purpose: Detect recurrence early, manage side effects, and monitor overall health

## **Doctor-Patient Conversation: Liposarcoma**

Doctor: Hello, thank you for coming in today. I have reviewed your biopsy and imaging results, and I want to discuss your diagnosis and next steps.

Patient: Okay, doctor. What did the tests show?

Doctor: The pathology confirms that you have liposarcoma, which is a type of cancer that arises from fat cells in soft tissues. It’s important we plan your treatment carefully to achieve the best outcome.

Patient: Do I need more tests?

Doctor: Yes. We will do additional imaging, such as an MRI or CT scan, to determine the exact size and location of the tumor and to check if it has spread, especially to the lungs. This will help us stage the cancer and plan treatment.

Patient: Can I have a copy of my pathology report?

Doctor: Absolutely. I will provide you with a copy of your pathology report. It contains detailed information about the tumor type and grade, which helps guide treatment decisions.

Patient: What are my treatment options?

Doctor: The main treatment is surgery to remove the tumor completely. Depending on the tumor’s size and location, radiation therapy may be given before or after surgery to reduce the risk of recurrence. Chemotherapy is sometimes used, especially for more aggressive types, but not all liposarcomas respond to it.

Patient: What are the potential risks of each treatment?

Doctor: Surgery carries risks such as infection, bleeding, and possible impact on nearby structures depending on the tumor’s location. Radiation can cause skin irritation and fatigue, and chemotherapy may cause nausea, hair loss, and increased infection risk. We will manage side effects carefully.

Patient: Can any treatments cure my cancer?

Doctor: Yes, many patients can be cured, especially if the tumor is removed completely and hasn’t spread. The prognosis depends on the tumor subtype, size, and whether it has metastasized.

Patient: Is there one treatment you think is best for me?

Doctor: Based on your tumor’s characteristics, I recommend surgery combined with radiation therapy. Chemotherapy is less likely to be beneficial in your case but can be considered if needed. We will tailor the plan to your situation.

Patient: If you had a friend or family member in my situation, what would you recommend?

Doctor: I would advise them to seek treatment at a specialized sarcoma center with a multidisciplinary team experienced in managing these tumors. Early and complete treatment offers the best chance for cure and preserving function.

Patient: How much time can I take to choose a treatment?

Doctor: While it’s important to start treatment promptly, you can take a few weeks to consider your options and ask questions. We will support you throughout this process.

Patient: How will cancer treatment affect my daily life?

Doctor: You may experience fatigue, pain, or limited mobility depending on the surgery site. Radiation and chemotherapy can cause additional side effects, but we have supportive care to help you manage these.

Patient: Should I see a specialist? What will that cost, and will my insurance cover it?

Doctor: Yes, seeing a sarcoma specialist at a specialized center is important. Costs and insurance coverage vary, but most insurance plans cover specialist consultations and treatments. We can help you with referrals and insurance questions.

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Patient: What would happen if I choose not to have treatment?

Doctor: Without treatment, the tumor will likely continue to grow and may spread, causing pain, functional problems, and potentially life-threatening complications. Early treatment offers the best chance for cure or control.

Patient: Thank you, doctor. This is a lot to take in, but I appreciate your help.

Doctor: I understand it’s overwhelming. Please feel free to ask any questions at any time. We’re here to support you every step of the way.

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### 

### **Chondrosarcoma**

A chondrosarcoma is a type of rare bone cancer that typically develops in cartilage — the flexible connective tissue that protects your joints and bones. Healthcare providers may call this condition a sarcoma.

This cancer can appear anywhere you have cartilage, but it usually forms in your:

* Arms and shoulder blades.
* Legs.
* Pelvis.
* Ribs.
* Sternum (breastbone).

They may also develop in benign bone tumors that become cancerous.

Chondrosarcomas are very rare, affecting 1 in 200,000 people in the U.S. You can develop a chondrosarcoma at any age, but the condition is more common in people ages 40 to 75, with most people receiving a diagnosis at age 51. The most common treatment is surgery to remove cancerous cartilage and bone.

#### **Types of chondrosarcomas**

There are several different types of chondrosarcomas. Chondrosarcomas that develop in cartilage are named for the cells that make up the tumors:

##### **Conventional chondrosarcoma**

This is the most common type, accounting for more than 85% of all chondrosarcomas. It typically affects people ages 50 to 70 and develops in your femur, humerus (upper arm bone) and pelvis. Conventional chondrosarcomas grow very slowly and are less likely to spread (metastasize) than other types.

##### **Dedifferentiated chondrosarcoma**

Dedifferentiated chondrosarcomas account for 10% of all chondrosarcomas. This type tends to develop in adults aged 60 and older and grows faster than most other chondrosarcomas. The fast-growing tumors usually develop in your humerus, femur or pelvic bones.

They’re known as dedifferentiated chondrosarcomas because some cells start out as typical chondrosarcomas, but then some parts of the tumor change into cells like those of a high-grade sarcoma. High-grade sarcomas are cancers that tend to grow and spread very quickly, including osteosarcoma, fibrosarcoma and undifferentiated pleomorphic sarcoma.

##### **Clear cell chondrosarcoma**

This type accounts for 2% of all chondrosarcomas. It typically affects people ages 30 to 50 but can affect people in their 20s. Clear cell chondrosarcomas are typically found near a joint in your arm or leg. They tend to grow slowly and rarely spread to other areas in your body.

##### **Mesenchymal chondrosarcoma**

This type often affects adults ages 19 to 30. It typically develops in your spine, ribs or jaw. Mesenchymal chondrosarcoma often grows quickly and is more likely to spread than other chondrosarcomas and come back (recur) after treatment.

Extraskeletal myxoid chondrosarcoma is a form of mesenchymal chondrosarcoma. It forms in the soft tissue in the upper part of your arms and legs but not in your bone or cartilage.

## **Symptoms and Causes**

Most chondrosarcomas grow slowly, causing symptoms that take months to develop. The most common symptoms are:

* Bone pain in a specific area of your body that comes and goes and gets worse at night.
* Swollen spot or lump on a bone, like on your arm, leg or ribs.
* Fatigue.
* Unintentional weight loss.

It’s important to remember that bone cancer is rare. Many chondrosarcoma symptoms are like the symptoms of other less serious issues. A lump on your leg may not indicate bone cancer.

But if you have a lump that doesn’t go away within two weeks or you feel exhausted all the time, talk to a healthcare provider. They’ll check your overall health to find out what’s causing your symptoms.

### **What causes chondrosarcoma?**

Researchers don’t know the exact cause but link the condition to genetic disorders, including:

* Li Fraumeni syndrome: People with this condition are likely to develop cancerous tumors, including chondrosarcomas.
* Maffucci syndrome and Ollier’s disease: These disorders cause benign tumors in your cartilage, bone and skin.
* Hereditary multiple osteochondromas: These are multiple benign bone tumors that can disrupt your bone growth.

In some cases, pathologists who study genetic changes in chondrosarcoma think a chromosomal change or certain genetic mutations that aren’t part of an inherited disorder may change cartilage cells.

### **Complications of this condition**

Fast-growing chondrosarcomas like mesenchymal chondrosarcoma or dedifferentiated chondrosarcoma can be life-threatening because they’re quick to spread and affect other areas of your body.

## **Diagnosis and Tests**

A healthcare provider will ask questions about your symptoms, including:

* When you first noticed them.
* If they’ve gotten worse.
* How they’ve affected your daily life.

They’ll do a physical examination and may order imaging tests or a biopsy.

#### **Imaging tests**

To diagnose chondrosarcomas, healthcare providers may order the following imaging tests:

* X-ray.
* Computed tomography (CT) scan.
* Magnetic resonance imaging (MRI) scan.
* Positron emission tomography (PET) scan.
* Bone scan.

#### **Biopsy**

Your provider may refer you to an orthopaedist, a surgeon who diagnoses and treats conditions including bone cancer, to do a biopsy. Your orthopaedist may do different types of biopsies to remove tissue from a suspicious lump so a pathologist can examine the tissue under a microscope. Those types are:

* Fine-needle aspiration: An orthopaedist uses a needle and syringe to get the tissue sample.
* Incisional biopsy: They cut into the tumor to remove a tissue sample.
* Excisional biopsy: They remove the entire lump or section of tissue.

A pathologist will examine the tissue sample for signs of cancerous cells. If cells are cancerous, they’ll identify the tumor type and establish a tumor grade.

### **What are the grades of chondrosarcomas?**

A tumor grade is a measure of how fast a tumor may grow and spread. Chondrosarcoma grades range from 1 (I) to 3 (III):

* Low-grade (grade I) chondrosarcomas: Also called atypical cartilaginous tumors, these tend to grow the slowest and are very unlikely to spread.
* Intermediate-grade (grade II) chondrosarcomas: These are slightly more likely to spread.
* High-grade (grade III) chondrosarcomas: These are the most likely to spread.

## **Management and Treatment**

Most of the time, you’ll need surgery to remove the chondrosarcoma. The specific surgery will depend on your situation, including what kind of chondrosarcoma you have, the tumor location and its grade, meaning how quickly it may spread. Surgeries for chondrosarcoma include:

* Curettage: In this procedure, your provider scrapes the tumor tissue from your bone and replaces the missing bone with bone graft material.
* Limb-sparing surgery: Your provider removes the tumor and nearby bone and muscle, followed by reconstructive surgery to replace the missing bone and tissue.

Very rarely, your orthopaedist may recommend surgery to remove part of your arm or leg (amputation). They may recommend you have a prosthetic limb. In all cases, you’ll have physical therapy to help you build strength, balance and mobility as you adapt to your situation.

If you have a rare type of chondrosarcoma like dedifferentiated or mesenchymal chondrosarcoma, you may have chemotherapy or radiation therapy before surgery to shrink the tumor, as well as after the surgery to kill any remaining cancer cells.

## **Outlook / Prognosis**

There are several types of chondrosarcomas, each with different prognoses or expected outcomes. Ask your healthcare provider what you can expect given your specific situation. They’ll be glad to explain your prognosis.

#### **Is there a cure for chondrosarcoma?**

In some cases, surgery to remove very small, slow-growing conventional chondrosarcoma tumors may cure the condition. Based on the type of chondrosarcoma, adding chemotherapy may help cure the condition.

#### **Chondrosarcoma survival rates**

Survival rates for chondrosarcoma vary depending on the tumor type and whether the tumor is spreading to other parts of your body. Overall, 79% of people with chondrosarcoma were alive five years after diagnosis. Here are specific survival rates based on tumor location:

| **Location** | **Five-year survival rate** |
| --- | --- |
| Local: There’s no sign of spreading from the bone where it started. | 91% |
| Regional: The tumor is spreading from your bone into nearby bones, tissues, organs or lymph nodes. | 76% |
| Distant: The tumor is in your lungs or in bones in other parts of your body. | 17% |

As you think about your situation, try to keep a few things in mind:

* A survival rate is an estimate, not a prediction. They’re estimates based on the experiences of other people, and your situation may be very different.
* Survival rate estimates reflect what happened in the past. For example, the survival rates listed above are based on what happened to people with chondrosarcoma between 2012 and 2018.
* Survival rates don’t indicate how long you’ll live.

If you have questions or concerns about what a survival rate estimate means in your case, ask your provider to explain how these estimates factor into your situation.

## **Prevention**

No, they can’t, partly because researchers don’t know exactly why they happen. Research shows people with certain inherited disorders have an increased risk of developing chondrosarcoma. Talk to a healthcare provider about your family medical history so they can assess your risk and recommend steps to monitor your health.

## **Living With**

Living with chondrosarcoma usually starts with recovering from treatment. Chondrosarcoma is often treated with surgery that might involve removing a limb or section of a limb to remove your cancer. Once you’ve recovered from surgery, you’ll need to start a rehabilitation program to help you adjust to using a prosthetic limb.

You might need help adjusting to other changes, such as how you go about your everyday life or changes in your appearance. Your healthcare provider will have suggestions for physical, occupational or mental health therapies that may help you manage these challenges.

### **When should I see my healthcare provider?**

Ask your provider to explain the kinds of changes in your body that may be signs that cancer has come back, and when it makes sense for you to contact them.

### **Common Questions**

### **What is the difference between chondrosarcoma and osteosarcoma?**

Osteosarcoma starts in the bone and typically affects children. Chondrosarcoma starts in your cartilage and typically affects adults. Healthcare providers may treat chondrosarcoma with surgery alone and treat osteosarcoma with chemotherapy and surgery.

## What kind of chondrosarcoma do I have?

Chondrosarcomas are classified into several subtypes according to the 2020 WHO classification. The main types include:

* Conventional chondrosarcoma (about 85-90% of cases), subdivided into:
  + Low-grade (grade 1)
  + High-grade (grades 2 and 3)
* Secondary peripheral chondrosarcoma
* Periosteal chondrosarcoma
* Dedifferentiated chondrosarcoma
* Mesenchymal chondrosarcoma
* Clear cell chondrosarcoma

Your exact subtype and grade depend on biopsy and imaging findings, which help determine aggressiveness and treatment approach.

## What treatments do you recommend?

* Surgery is the primary treatment for most chondrosarcomas, aiming for complete removal with clear margins.
* Radiation therapy is generally less effective but may be considered in inoperable cases or certain subtypes like mesenchymal chondrosarcoma.
* Chemotherapy is usually not effective for conventional chondrosarcoma but may be used for aggressive subtypes such as mesenchymal or dedifferentiated chondrosarcoma.
* Treatment plans are individualized based on subtype, grade, and tumor location.

## Why do you recommend those treatments?

* Surgery offers the best chance for cure by physically removing the tumor.
* Conventional chondrosarcomas are relatively resistant to chemotherapy and radiation, so surgery is the mainstay.
* More aggressive or rare subtypes (mesenchymal, dedifferentiated) may respond better to chemotherapy, thus it is added in those cases.
* Radiation may be used when surgery is not feasible or to reduce local recurrence risk.

## What are the treatment side effects?

* Surgery: Risks include infection, bleeding, nerve or tissue damage, and functional impairment depending on tumor location and extent of surgery.
* Radiation therapy: Can cause local skin irritation, fatigue, and potential long-term damage to nearby tissues.
* Chemotherapy: Side effects vary by regimen but often include nausea, fatigue, hair loss, and increased infection risk.

## What are the outcomes of this treatment?

* For low-grade conventional chondrosarcoma, surgery alone often achieves good long-term control with low recurrence.
* Higher-grade tumors have a higher risk of recurrence and metastasis, leading to lower survival rates.
* Rare aggressive subtypes (dedifferentiated, mesenchymal) have poorer prognosis despite multimodal treatment.
* Overall survival varies widely by subtype and grade; for example, median survival for dedifferentiated chondrosarcoma is about 11 months, whereas juxtacortical subtype median survival can be over 8 years.

## If I have the recommended treatments, can my chondrosarcoma come back?

* Yes, local recurrence is possible, especially if surgical margins are not clear or for higher-grade tumors.
* Metastasis risk increases with tumor grade and subtype.
* Regular follow-up with imaging is essential to detect recurrence early.
* The risk of recurrence varies by subtype and grade but can be significantly reduced with appropriate surgery and, when indicated, additional therapies

## **Diagnostic Considerations**

In addition to the conditions listed in the differential diagnosis, the following problems should be considered:

* Fibrous histiocytoma
* Metastatic carcinoma
* Paget sarcoma

## **Differential Diagnoses**

* Chondroblastoma
* Chondroma
* Chondromyxoid Fibroma
* Chordoma
* Fibrosarcoma
* Osteofibrous Dysplasia
* Osteosarcoma
* Synovial Chondromatosis

## 

## **Epidemiology**

### Frequency by tumor type

Conventional central chondrosarcomas account for nearly 80-90% of all chondrosarcomas and 20-27% of all primary bone sarcomas.They demonstrate a predilection for the axial skeleton. Rates of involvement are as follows:

* Pelvis and ribs, 45%
* Ilium, 20%
* Femur, 15%
* Humerus, 10%
* Others, 10%

The spine and the craniofacial bones are rarely involved.

Dedifferentiated chondrosarcomas are responsible for as many as 10% of all chondrosarcomas. The femur is the site most commonly involved, accounting for one-third of all dedifferentiated chondrosarcomas. The other sites of involvement are the pelvis (20%), the humerus (16%), the ribs (7%), and the scapula (7%).

Clear cell chondrosarcomas account for fewer than 5% of all chondrosarcomas. They have a predilection for the ends of long tubular bones, involving the epiphysis. Like chondroblastomas, these lesions extend to involve the articular cartilage. The proximal aspect of the femur is the site most often affected (45%), followed by the proximal portion of the humerus.

Fewer than 2% of all chondrosarcomas are mesenchymal chondrosarcomas. The maxilla and the mandible are the most common sites of involvement, followed by the vertebrae, the ribs, the pelvis, and the humerus. The appendicular skeleton is rarely involved.

Juxtacortical chondrosarcomas are rare and generally involve the surface of the diaphysis or metaphysis of long tubular bones.

### Age-, sex-, and race-related demographics

Incidences do not differ among ethnic groups. Sex and age distributions are listed in Table 1 below.

Table 1. Sex Ratios and Ages of Peak Incidence for Different Types of Chondrosarcoma

| Chondrosarcoma | Male-to-Female Ratio | Age of Peak Incidence |
| --- | --- | --- |
| Conventional | Almost 1:1 (slight male predominance) | 50-70 y (most common >50 y, gradual increase with age) |
| Dedifferentiated | Similar to the ratio above | >50 y |
| Clear cell | 2.4:1 | 20-40 y (common 10-90 y) |
| Mesenchymal | 1:1 | 20-30 y (common in teenagers and young adults) |
| Juxtacortical | 1:1 | 20-40 y |

Chondrosarcomas are considerably rarer in children and adolescents than in adults

## Staging

The Enneking staging system for musculoskeletal sarcomas is applicable to chondrosarcomas, as follows [23] :

* Stage I (low-grade tumor) - I-A, intracompartmental; I-B, extracompartmental
* Stage II (high-grade tumor) - II-A, intracompartmental; II-B, extracompartmental
* Stage III (distant metastasis)

## **Guidelines for Treatment of Chondrosarcoma**

NCCN recommendations for treatment of chondrosarcoma are as follows:

* Wide excision, if the lesion is resectable; wide excision should provide negative surgical margins and may be achieved by either limb-sparing surgery or amputation
* Radiation therapy (RT) may be considered for unresectable and borderline resectable tumors
* Postoperative treatment with proton and/or photon beam radiation for tumors in unfavorable location
* No established chemotherapy regimens exist for grade I-III tumors, but ivosidenib is an option for susceptible IDH1 mutations
* For dedifferentiated chondrosarcoma, treatment should follow osteosarcoma guidelines; ivosidenib may occasionally be useful
* For mesenchymal tumor, treatment should follow Ewing sarcoma guidelines
* For metastatic and widespread disease, dasatinib and pazopanib are recommended regimens

NCCN recommendations for treatment of local recurrence of chondrosarcoma are as follows:

* Wide excision if the lesion is resectable
* If margins are positive after wide excision, consider RT or re-resection to achieve negative surgical margins
* RT for unresectable recurrences

NCCN recommendations for systemic recurrences/metastatic chondrosarcoma are as follows:

* Oligometastatic disease - Surgically excise all sites if possible; consider RT for unresectable sites; consider entry into a clinical trial
* Widespread disease - Consider RT, surgery, ablative or a combination thereof for symptomatic sites; consider systemic therapy; consider entry into a clinical trial

## **genetic Alterations in Chondrosarcoma**

* IDH1 and IDH2 mutations are the most common somatic alterations, found in approximately 34-50% of conventional chondrosarcomas and up to 60% in some aggressive subtypes like undifferentiated chondrosarcoma.
* These mutations affect enzymes involved in the tricarboxylic acid cycle, leading to accumulation of the oncometabolite 2-hydroxyglutarate (2HG), which causes epigenetic changes that promote tumor development.
* TP53 mutations occur in about 22-28% of conventional chondrosarcomas and are more frequent in higher-grade and dedifferentiated subtypes (up to 68% in dedifferentiated chondrosarcoma).
* Other common alterations in dedifferentiated chondrosarcoma include mutations or deletions in TERT (65%), CDKN2A/CDKN2B (around 35%), and PDGFRB mutations (13%).
* HEY1-NCOA2 gene fusions are characteristic of mesenchymal chondrosarcoma (about 87% of cases).
* Mutations in COL2A1, the gene encoding type II collagen, are present in about 37% of chondrosarcomas and may disrupt cartilage differentiation and extracellular matrix deposition.
* No cases showed high microsatellite instability (MSI), and tumor mutational burden (TMB) is generally low, indicating limited response to immunotherapy, although some dedifferentiated and mesenchymal subtypes express PD-L1

## **Doctor-Patient Conversation: Chondrosarcoma**

Doctor: Hello, thank you for coming in today. I have reviewed your biopsy and imaging results, and I’d like to discuss your diagnosis and treatment options.

Patient: Okay, doctor. What did the tests show?

Doctor: The pathology confirms that you have chondrosarcoma, which is a type of cancer that develops in the cartilage cells of your bone. There are different subtypes and grades, which affect how aggressive the tumor is and how we treat it.

Patient: What kind of chondrosarcoma do I have?

Doctor: Based on your biopsy, you have a conventional chondrosarcoma, which is the most common type. It’s graded as intermediate in aggressiveness, which means it requires careful treatment but can often be managed effectively.

Patient: What treatments do you recommend?

Doctor: The primary treatment is surgery to remove the tumor completely with clear margins. Because chondrosarcoma tends to be resistant to chemotherapy and radiation, these treatments are usually not the first choice unless surgery isn’t possible or for certain aggressive subtypes.

Patient: Why do you recommend surgery?

Doctor: Surgery offers the best chance to remove all the cancer cells and reduce the risk of the tumor coming back. Since chemotherapy and radiation are less effective for this type, surgery is the cornerstone of treatment.

Patient: What are the side effects of surgery?

Doctor: Side effects depend on the tumor’s location and the extent of surgery. They may include pain, swelling, risk of infection, and possible impact on bone strength or nearby nerves. We will work with you on rehabilitation and pain management.

Patient: What are the outcomes of this treatment?

Doctor: For intermediate-grade conventional chondrosarcoma, surgery can often control the disease well, with a good chance of long-term survival if the tumor is completely removed. However, regular follow-up is important to monitor for recurrence.

Patient: If I have the surgery, can the cancer come back?

Doctor: There is always a risk of recurrence, especially if any cancer cells remain after surgery. That’s why achieving clear surgical margins is important, and why we will schedule regular follow-ups with imaging to detect any recurrence early.

Patient: What if surgery isn’t an option?

Doctor: If surgery isn’t feasible, we may consider radiation therapy to control the tumor, but it’s generally less effective. For rare aggressive subtypes, chemotherapy might be used. We’ll tailor the treatment to your specific case.

Patient: Thank you, doctor. This helps me understand what to expect.

Doctor: You’re welcome. Please feel free to ask any questions as we go along. We’re here to support you throughout your treatment.

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