Tab 1

**Oncology 2**

**Lip cancer**

Lip cancer occurs when abnormal cells grow out of control, resulting in tumors (solid tissue masses) or lesions (abnormal areas of skin) on your lips. Most lip cancers (about 90%) are squamous cell carcinoma. This type of cancer starts in the cells located in your skin’s outer layer. Less common types are basal cell carcinoma and melanoma.

Lip cancer can develop on either your upper or lower lip, but it’s more likely to start on your lower lip. The most common sign is a sore, blister, ulcer or lump on your bottom lip that won’t go away.

Lip cancer is the most common type of oral (mouth) cancer but makes up less than 1% of all cancer diagnoses total in the United States. Only about .1% of people in the U.S. will get diagnosed with lip cancer at some point in their lives.

**Symptoms and Causes**

Early-stage lip cancer often looks like a mouth sore that won’t heal. It’s easy to mistake tumors for cold sores when they first appear. The difference is that cold sores go away on their own in about 10 days. But lip cancer lesions linger.

Other signs of lip cancer include:

* A flat or slightly raised colored spot on your lips (may appear white or reddish on light skin or dark brown or gray on dark skin).
* Pain, numbness or tingling on your lips or in your mouth.
* Loose teeth. (If you wear dentures, you may notice changes in how they fit.)
* Bleeding or thickening lips.
* A swollen jaw.

**What causes lip cancer?**

Experts don’t know exactly what causes lip cancer. As with all cancers, errors in cell DNA cause normal cells to become cancer cells that multiply out of control. The abnormal cancer cells can spread and damage healthy tissue. Experts haven’t identified one single reason why cells behave this way. But they’ve identified several risk factors that people who get lip cancer share. Most have to do with lifestyle and environment.

**Risk factors**

Risk factors for lip cancer include:

* Tobacco use. This includes smoking cigarettes, cigars and pipes, and using snuff and chewing tobacco. Most lip cancers are linked to tobacco use.
* Heavy alcohol use. You increase your risk of lip cancer by up to 30 times if you use tobacco and also consume excessive amounts of alcohol.
* Excessive sun exposure. This includes exposure to artificial light in tanning beds.
* Having fair skin. People who are white with light features are most at risk.
* Being over 40. Most people get lip cancer in their 50s and 60s.
* Sex. Males are up to three times more likely to develop lip cancer.
* Having a weakened immune system.

**Diagnosis and Tests**

Often, dentists or dermatologists spot lip cancer during routine exams. If a healthcare provider suspects lip cancer, they’ll ask about your medical history and habits, like whether you smoke. They may recommend diagnostic tests, including:

* Physical exam. Your healthcare provider will examine your lip and ask about your symptoms. They’ll also look at your mouth, face and neck to check for signs that the cancer has spread beyond your lips.
* Soft tissue biopsy. Your provider will remove a small sample of the affected tissue and send it to a pathology lab for testing. Results can show if a lesion or tumor is lip cancer.

If biopsy results show you have cancer, your healthcare provider may order additional tests to see if it’s spread. Advanced lip cancers metastasize or spread to distant parts of your body. The good news is that most people get diagnosed before lip cancer spreads.

Tests include:

* Imaging tests. Your healthcare provider may take a CT (computed tomography) scan, a PET scan or use magnetic resonance imaging (MRI) to check for tumors.
* Endoscopy. During this procedure, your provider passes a small, flexible camera down your throat while you’re sedated to look for signs of cancer.

**Management and Treatment**

The best treatment for you depends on the size of the tumor or lesion and the cancer stage. Often, healthcare providers can treat precancerous lip cancer (abnormal lesions that may become malignant) and early-stage lip cancer with surgery alone. You may need a combination of treatments if your condition is more advanced.

Lip cancer treatments include:

* Surgery. Your surgeon removes the lesion or tumor and repairs your lip. They may also remove lymph nodes in your neck if they suspect the cancer has spread there.
* Radiation therapy. This treatment uses radiation to kill cancer cells. Your provider may recommend external beam radiation therapy (EBRT) or brachytherapy (internal radiation therapy). Radiation therapy may be a standalone treatment, or you may need it after surgery to eliminate any remaining cancer cells.
* Chemotherapy. This treatment uses drugs to kill cancer cells. You may need chemo combined with radiation therapy. If your lip cancer has spread and no other treatments are available, your provider may recommend chemotherapy to ease your symptoms (palliative care).
* Targeted therapy. This treatment targets specific cancer cell genes and proteins, destroying them. People with lip cancer usually get it in combination with chemo.
* Immunotherapy. These drug treatments boost your body’s immune system and help it fight off cancer cells. For lip cancer, most people get immunotherapy when the cancer is advanced and other treatments aren’t an option.

**Complications regarding lip cancer treatment**

If you had surgery to remove a large tumor, you may need reconstructive surgery so your mouth looks like it did before. You may also need to work with a speech-language pathologist if you’re having trouble speaking or swallowing afterward.

If you’re worried about how you’ll look after surgery, remember that several procedures can help restore your appearance. Discuss your options with your healthcare provider before surgery to remove the tumor, so you know what to expect.

**How soon after treatment will I feel better?**

Recovery depends on several factors, including what type of treatment you get and how your body heals. People with early-stage lip cancer who have surgery typically recovered within a few weeks. If you get radiation therapy or chemotherapy, it may take several months to fully feel like yourself again.

**Outlook / Prognosis**

Lip cancer is more predictable when you get treatment in the early stages, before it spreads. With an early diagnosis, you’ll likely need surgery to remove the lesion. Your healthcare provider may recommend chemotherapy, radiation therapy or other cancer treatments if the cancer cells have spread to other areas of your body.

Your healthcare provider can explain what to expect based on your diagnosis.

**Does lip cancer spread quickly?**

Squamous cell carcinoma (the most common type of lip cancer) tends to spread slowly. As it’s easy to see, most people notice the unusual growths on their lip and get checked before the cancer spreads.

Still, it can spread without treatment. See a healthcare provider if you’re noticing changes that you’re unsure about.

**Is lip cancer fatal?**

Not usually. Because lip cancer lesions develop in easily seen locations, this type of cancer is detected and treated early in most cases. As a result, lip cancer has an overall five-year survival rate of 91%. This means that 91% of people diagnosed with the condition are still alive five years later.

Keep in mind that survival rates are estimates. They can’t offer details about your case or tell you how long you’ll live. If you have more questions about survival rates, ask your healthcare provider.it

**Prevention**

Reduce your risk for lip cancer by avoiding common risk factors:

* Don’t use tobacco. Tobacco use is the leading risk factor for lip cancer and cancers of the mouth. If you smoke, consider quitting.
* Avoid heavy alcohol use. If you drink, do so in moderation. This means no more than two drinks a day for males, and no more than one drink daily for females.
* Protect yourself from the sun. Apply lip balm and sunscreen that’s at least SPF 30 anytime you’re outside (even on cloudy days). Whenever possible, plan outdoor activities outside the hours when you’re most likely to get direct sunlight. In the United States, you’ll get more sun exposure between 10:00 a.m. and 4:00 p.m.
* Avoid tanning beds. Steer clear of tanning beds, which can increase your risk of lip and skin cancer.
* Get routine oral cancer screenings. Your primary care physician or dentist can perform these screenings to check for abnormalities.

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

You should schedule a visit with a healthcare provider if you notice changes in the skin on your lips. If you develop a sore on your lip that lasts for more than two weeks, call a provider right away.

**Additional Common Questions**

**Can you kiss someone with lip cancer?**

Absolutely. You can kiss a loved one with lip cancer without putting your health at risk. Cancer happens because of problems with cell DNA inside a person’s body. You can’t catch it by hugging or kissing.

What stage of lip cancer do I have?

Lip cancer staging depends on tumor size, depth of invasion, lymph node involvement, and spread:

* Stage 0: Cancer cells are only in the top layer of lip tissue (carcinoma in situ).
* Stage 1: Tumor is ≤ 2 cm and invades ≤ 5 mm deep; no lymph node involvement.
* Stage 2: Tumor is > 2 cm but ≤ 4 cm, or ≤ 2 cm with invasion > 5 mm but ≤ 10 mm; no lymph nodes affected.
* Stage 3: Tumor > 4 cm or any size tumor with one lymph node ≤ 3 cm involved.
* Stage 4: More advanced local invasion (bone, nerves, nearby structures), multiple or large lymph nodes involved, or distant metastases.

Your exact stage is determined by your tumor size, depth, and whether lymph nodes or distant sites are involved.

Has the cancer spread beyond my lips?

* If your cancer is Stage 0, 1, or 2, it usually has not spread beyond the lips.
* Stage 3 or higher indicates possible spread to nearby lymph nodes or adjacent tissues.
* Stage 4 means the cancer has invaded nearby structures like bone or nerves or spread to distant organs.

Your doctor will use imaging and physical exams to determine if there is any spread.

What are my treatment options?

* Surgery to remove the tumor is the most common and effective treatment for early-stage lip cancer.
* Radiation therapy may be used alone or after surgery, especially if margins are close or lymph nodes are involved.
* Chemotherapy is less commonly used but may be recommended for advanced or metastatic cases.
* Treatment choice depends on cancer stage, location, and your overall health.

What side effects should I expect?

* Surgery: Pain, swelling, changes in lip appearance or function, possible numbness.
* Radiation: Skin irritation, dryness, soreness, possible changes in taste or saliva.
* Chemotherapy: Fatigue, nausea, hair loss, increased infection risk.
* Side effects vary based on treatment type and extent.

How will treatment affect my daily life?

* Early-stage treatment often allows a quick return to normal activities.
* Surgery or radiation may temporarily affect eating, speaking, and appearance.
* Advanced treatments may require more recovery time and supportive care.
* Your care team will help manage side effects to maintain quality of life.

Will I be able to work while getting treatment?

* Many patients with early-stage lip cancer can continue working during treatment or take short breaks.
* More extensive surgery or combined therapies may require longer time off work.
* Your ability to work depends on treatment type, side effects, and your job’s physical demands.

**EPIDEMIOLOGY**

Incidence and Demographics

* The rate of new lip cancer cases in the U.S. is approximately 0.5 per 100,000 persons per year (age-adjusted) based on 2017–2021 data.
* Lip cancer is more common in men than women:
* Males: about 0.7 per 100,000
* Females: about 0.3 per 100,000.
* The majority of lip cancers occur on the lower lip (85–95%), with fewer cases on the upper lip or lip commissure.
* Lip cancer is most frequently diagnosed in older adults, with the median age at diagnosis around 70 years.
* Incidence increases with age, with the highest proportion of cases in people aged 65–74 years.

Risk Factors

* Major risk factors include:
* Tobacco use
* Heavy alcohol consumption
* Chronic sun (UV) exposure, including artificial sources like tanning beds.
* Men have higher exposure to these risk factors, contributing to higher incidence.

Geographic and Ethnic Variation

* Incidence varies by race/ethnicity:
* Highest rates in Non-Hispanic White populations (0.9 per 100,000 in males).
* Lower rates in Non-Hispanic Black and Asian/Pacific Islander groups (~0.1 per 100,000).
* Globally, lip and oral cavity cancers show increasing incidence in many countries, especially in BRICS nations (Brazil, Russia, India, China, South Africa), with significant rises in India and China.

Mortality

* The death rate from lip cancer is low, about 0.02 per 100,000 persons per year in the U.S..
* Prognosis is generally favorable compared to other oral cancers, especially when diagnosed early.

**DIFFERENTIAL DIAGNOSIS**

Benign and Precancerous Conditions

* Actinic cheilitis: A precancerous condition caused by sun damage, presenting as scaly, crusted, or rough patches on the lip.
* Herpes labialis (cold sores): Recurrent painful vesicles that heal spontaneously within 7-10 days.
* Mucocele: A benign mucous cyst appearing as a soft, translucent swelling.
* Traumatic ulcers: Resulting from mechanical irritation or injury.
* Fordyce spots: Small, painless sebaceous gland spots seen on the vermillion border.
* Benign tumors: Such as papillomas, lipomas, or fibromas.
* Leukoplakia and erythroplakia: White or red patches that can be precancerous or early cancer.

Malignant Lesions

* Squamous cell carcinoma (SCC): The most common type of lip cancer, often presenting as a persistent ulcer, nodule, or crusted lesion.
* Basal cell carcinoma: Less common on the lip but can occur, typically on the lower lip.
* Melanoma: Rare but aggressive cancer presenting as pigmented or nonpigmented lesions.
* Verrucous carcinoma: A well-differentiated variant of SCC with a warty appearance.
* Lymphoma: May present as a mass or ulcer on the lip.
* Minor salivary gland tumors: Such as mucoepidermoid carcinoma or adenoid cystic carcinoma.

Infectious and Inflammatory Conditions

* Herpetic gingivostomatitis: Acute viral infection causing painful ulcers.
* Oral candidiasis: Fungal infection causing white plaques.
* Contact dermatitis: Allergic or irritant reactions causing lip inflammation.

**Key Diagnostic Approaches**

**STAGES**

Once a biopsy and all imaging studies are complete, lip cancer is given a stage.

Stage I

This is an early stage of cancer, and the tumor on the lip is less than 2 centimeters in size and has not spread into local lymph nodes.

Stage II

Still an early-stage lip cancer, the tumor is between 2 and 4 centimeters in size and has not spread into local lymph nodes.

Stage III

A more advanced stage of cancer, the tumor is more than 4 centimeters in size or is any size and has spread into lymph nodes in the neck.

Stage IV

In this stage of cancer, the original lip tumor may be any size but has either spread into other nearby tissues (such as the jaw), has spread into multiple lymph nodes on the same side of the neck, has spread into any lymph node on the opposite side of the neck, or has spread into other organs in the body.

**Doctor-Patient Conversation: Lip Cancer**

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 lip cancer, specifically squamous cell carcinoma, which is the most common type. It’s important we talk about the stage and how we can treat it effectively.

Patient: What stage is my cancer? Has it spread beyond my lips?

Doctor: Based on your scans, the tumor is localized to your lower lip, and there is no evidence that it has spread to nearby lymph nodes or other parts of your body. This means it is an early-stage cancer, which is good news.

Patient: What treatment options do I have?

Doctor: The primary treatment is surgery to remove the tumor, aiming for clear margins to reduce the chance of recurrence. Depending on the size and location, we may also consider radiation therapy, especially if surgery margins are close or if lymph nodes become involved. Chemotherapy is usually reserved for more advanced cases.

Patient: What side effects should I expect from these treatments?

Doctor: Surgery may cause temporary pain, swelling, and changes in lip appearance or movement, but most patients recover well. Radiation can cause skin irritation, dryness, or soreness around the treated area. We will provide support to manage any side effects.

Patient: How will treatment affect my daily life? Will I be able to work?

Doctor: Many patients with early-stage lip cancer can continue their daily activities and work during treatment or take short breaks. Some recovery time may be needed after surgery, but we will tailor the plan to your needs and help you maintain your quality of life.

Patient: Are there resources where I can learn more?

Doctor: Yes, I will give you brochures with information about lip cancer and treatment. Trusted websites include the American Cancer Society and the Mouth Cancer Foundation. We can also connect you with support groups and counseling services.

Patient: What happens if I choose not to have treatment?

Doctor: Without treatment, the cancer is likely to grow and may spread to nearby tissues or lymph nodes, causing more serious health problems. Early treatment gives you the best chance for cure and preserving function.

Patient: Thank you, doctor. This helps me understand what to expect.

Doctor: You’re welcome. Please write down any questions you have, and bring a family member or friend to your next appointment if you like. We’re here to support you every step of the way.

REFERENCES

https://seer.cancer.gov/statfacts/html/lip.html

[Lip Cancer: Symptoms, Stages & Treatment](https://my.clevelandclinic.org/health/diseases/21933-lip-cancer#overview)

**MOUTH CANCER**

**DEFINITION AND DESCRIPTION**

Mouth cancer is a growth of cells that starts in the mouth. Mouth cancer can happen in any of the parts that make up the mouth. Mouth cancer can occur on the:

* Lips.
* Gums.
* Tongue.
* Inner lining of the cheeks.
* Roof of the mouth.
* Floor of the mouth.

The mouth also is called the oral cavity. Cancer that happens in the mouth is sometimes called oral cancer or oral cavity cancer.

Mouth cancer is one of several cancers that are considered to be types of head and neck cancer. Mouth cancer and other head and neck cancers often have similar treatments.

**Causes**

It's not always clear what causes mouth cancer. This cancer starts as a growth of cells in the mouth. It most often starts in cells called squamous cells. These are flat, thin cells that line the lips and the inside of the mouth. Most oral cancers are squamous cell carcinomas.

Mouth cancer happens when cells on the lips or in the mouth 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, the 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 mouth cancer include:

**Using tobacco**

All forms of tobacco increase the risk of mouth cancer. This includes cigarettes, cigars, pipes, chewing tobacco and snuff.

**Drinking alcohol**

Frequent and heavy drinking increases the risk of mouth cancer. Using alcohol and tobacco together increases the risk even more.

**Excessive sun exposure to the lips**

Ultraviolet light from the sun and tanning lamps increases the risk of lip cancer.

**Being exposed to human papillomavirus**

Human papillomavirus, also called HPV, is a common virus that's passed through sexual contact. For most people, it causes no problems and goes away on its own. For others, it causes changes in the cells that can lead to many types of cancer, including mouth cancer.

**A weakened immune system**

If the body's germ-fighting immune system is weakened by medicines or illness, there might be a higher risk of mouth cancer. People with a weakened immune system include those taking medicines to control the immune system, such as after an organ transplant. Certain medical conditions, such as infection with HIV, also can weaken the immune system.

**SYMPTOMS**

Signs and symptoms of mouth cancer may include:

* A lip or mouth sore that won't heal.
* A white or reddish patch on the inside of the mouth.
* Loose teeth.
* A growth or lump inside the mouth.
* Mouth pain.
* Ear pain.
* Difficult or painful swallowing.

**When to see a doctor**

Make an appointment with a doctor, dentist or other healthcare professional if you have any symptoms that worry you.

Mouth cancer diagnosis might start with an exam of the lips and mouth. A healthcare professional might remove a sample of tissue for testing to see if you have mouth cancer.

**Mouth cancer exam**

**Leukoplakia**

In a physical exam for mouth cancer, a healthcare professional looks at and feels your lips and mouth. That person checks for any lumps and areas of irritation. White patches in the mouth, called leukoplakia, and sores may be early signs of cancer.

**Mouth cancer biopsy**

If something concerning is found in an exam, the next step might be a mouth cancer biopsy. A biopsy is a procedure to remove a sample of tissue for testing in a lab. For a mouth cancer biopsy, a healthcare professional may use a cutting tool to cut away some concerning tissue from the mouth.

In the lab, tests can check the tissue for signs of cancer. Other tests might look for changes in the DNA inside the cancer cells. Results from these tests may help your healthcare team make a treatment plan.

**Mouth cancer staging**

Your healthcare team may do other tests to see if the cancer has spread beyond the mouth. Your healthcare team may use the results of these tests to give your cancer a stage. The stage tells your healthcare team about the extent of the cancer and about the prognosis. It also helps guide the treatment plan.

Mouth cancer staging tests may include:

* **Using a small camera to look at the throat.** During a procedure called endoscopy, a healthcare professional passes a thin, flexible tube equipped with a camera down the throat. The procedure helps the health professional look for signs that cancer has spread beyond the mouth.
* **Imaging tests.** A variety of imaging tests may help check whether cancer has spread beyond the mouth. Imaging tests may include X-ray, CT, MRI and positron emission tomography scans, also called PET scans. Not everyone needs each test. Your healthcare team decides which tests are needed based on your condition.

Mouth cancer stages range from 0 to 4. The lowest stages mean the cancer is small and hasn't grown very deep into the tissue in the mouth. As the cancer grows larger and grows deeper into the tissue, the stages get higher. A stage 4 mouth cancer can mean the cancer has grown very large or has spread to the lymph nodes. Stage 4 mouth cancer also can mean the cancer has spread to other parts of the body.

**Treatment**

Treatments for mouth cancer include surgery, radiation therapy and medicines. Medicines that help treat mouth cancer include chemotherapy, targeted therapy and immunotherapy. You may have just one type of treatment, or you may undergo a combination of cancer treatments.

Your healthcare team considers many factors when creating a mouth cancer treatment plan. These may include the cancer's location and how fast it's growing. The team also may look at whether the cancer has spread to other parts of the body and the results of tests on the cancer cells. Your team also considers your overall health and personal preferences.

**Surgery to remove mouth cancer**

During mouth cancer surgery, the surgeon removes the cancer and some of the healthy cells around it, called a margin. Removing the margin helps ensure that all the cancer cells are removed. The extent of the surgery depends on the size of the cancer. If cancer has spread into bone, the surgeon may remove some bone tissue.

Surgery carries a risk of bleeding and infection. Surgery for mouth cancer may affect your appearance. It also may affect the ability to speak, eat and swallow. Physical therapy and other rehabilitation services can help you cope with these changes.

You may need a tube to help you eat, drink and take medicine. For short-term use, the tube may be inserted through the nose and into the stomach. Longer term, a tube may be inserted through the skin and into the stomach.

**Surgery to reconstruct the mouth**

Reconstructive surgery may be needed when parts of the face, jaw or neck are removed during surgery. Healthy bone or tissue may be taken from other parts of the body and used to fill gaps left by the cancer. This tissue can replace part of the lip, tongue, palate or jaw, face, throat, or skin. Dental implants also may be used to replace your natural teeth.

If reconstruction is used to replace parts of the mouth, it usually is done at the same time as surgery to remove the cancer.

**Surgery to remove lymph nodes in the neck**

When mouth cancer spreads, it often goes to the lymph nodes in the neck first. If there are signs that the cancer has spread to the lymph nodes, you might need surgery to remove some lymph nodes, called a neck dissection. Even if there are no signs of cancer in the lymph nodes, you may have some of them removed as a precaution. Removing the lymph nodes removes the cancer and helps your healthcare team decide if you need other treatments.

To get to the lymph nodes, the surgeon makes a cut in the neck and removes the lymph nodes through the opening. The lymph nodes are tested for cancer. If cancer is found in the lymph nodes, other treatment might be needed to kill any cancer cells that are left. Options might include radiation or radiation combined with chemotherapy.

Sometimes the surgeon will remove only a few lymph nodes for testing. This is called a sentinel lymph node biopsy. In a sentinel lymph node biopsy, the surgeon removes the first few nodes into which a cancer may have spread. The lymph nodes are tested for cancer. If there's no cancer detected, it's likely that the cancer hasn't spread. Sentinel node biopsy isn't an option for everyone with mouth cancer. It's only used in some situations.

**Radiation therapy for mouth cancer**

Radiation therapy treats cancer with powerful energy beams. The energy can come from X-rays, protons or other sources. Radiation therapy for mouth cancer is most often delivered by a machine that moves around the body. The machine aims radiation to precise points. This kind of radiation therapy is called external beam radiation.

Sometimes radiation therapy for mouth cancer involves placing radioactive material inside the body. This kind of radiation therapy is called brachytherapy.

Radiation therapy might be the only treatment needed if the mouth cancer is very small. More often, radiation therapy is used after surgery. It can help kill any cancer cells that might remain. Sometimes radiation therapy may be combined with chemotherapy. This combination increases the effectiveness of radiation therapy. It also increases the risk of side effects.

If the cancer grows large or spreads to other parts of the body, radiation therapy may help relieve pain and other symptoms caused by the cancer.

The side effects of radiation therapy to the mouth may include dry mouth, tooth decay and damage to the jawbone.

You may need to see a dentist before radiation therapy starts to be sure your teeth are as healthy as possible. Any unhealthy teeth may need treatment or removal. A dentist can also help you understand how best to care for your teeth during and after radiation therapy to reduce your risk of complications.

**Chemotherapy for mouth cancer**

Chemotherapy treats cancer with strong medicines. Chemotherapy is often used after surgery to kill any cancer cells that remain. Chemotherapy may increase the effectiveness of radiation therapy, so the two treatments are often combined. If the cancer spreads to other parts of the body, chemotherapy can help control it.

The side effects of chemotherapy depend on which medicines you receive. Common side effects include nausea, vomiting and hair loss. Ask your healthcare team which side effects are likely for the chemotherapy medicines you'll receive.

**Targeted therapy for mouth cancer**

Targeted therapy for cancer is a treatment that uses medicines to attack specific chemicals in the cancer cells. By blocking these chemicals, targeted therapy can cause cancer cells to die.

For mouth cancer, targeted therapy may be used alone or in combination with chemotherapy or radiation therapy. It might be used after surgery to kill any cancer cells that remain. It also can help control a cancer that comes back or that spreads to other parts of the body.

**Immunotherapy for mouth 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.

For mouth cancer, immunotherapy might be used when mouth cancer comes back or spreads to other parts of the body.

**Prevention**

There's no proven way to prevent mouth cancer. However, you may reduce your risk of mouth cancer if you:

**Don't use tobacco**

If you don't use tobacco, don't start. If you currently use tobacco of any kind, talk with your healthcare team about strategies to help you quit.

**Limit alcohol intake**

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.

**Avoid excessive sun exposure to your lips**

Protect the skin on your lips from the sun by staying in the shade when possible. Wear a broad-brimmed hat that shades your entire face, including your mouth. Apply a sunscreen lip product for sun protection.

**Consider the HPV vaccine**

Receiving a vaccination to prevent HPV infection may reduce your risk of HPV-related cancers, such as mouth cancer. Ask your healthcare team whether the HPV vaccine is appropriate for you.

**Have regular health and dental exams**

During your appointments, your dentist, doctor or other member of your healthcare team can check your mouth for signs of cancer.

**Lifestyle and home remedies**

**Quit using tobacco**

Mouth cancers are closely linked to tobacco use, including cigarettes, cigars, pipes, chewing tobacco and snuff, among others. Not everyone who is diagnosed with mouth cancer uses tobacco. But if you do, now is the time to stop because:

* Tobacco use makes treatment less effective.
* Tobacco use makes it harder for the body to heal after surgery.
* Tobacco use increases the risk of a cancer recurrence and of getting another cancer in the future.

Quitting smoking or chewing can be very difficult. And it's that much harder when you're trying to cope with a stressful situation, such as a cancer diagnosis and treatment. Talk with your healthcare team about your options. This might include medicines, nicotine replacement products and counseling.

**Quit drinking alcohol**

Alcohol, particularly when combined with tobacco use, greatly increases the risk of mouth cancer. If you drink alcohol, stop drinking all types of alcohol. This may help reduce your risk of a second cancer.

**Alternative medicine**

No alternative medicine treatments have been found to cure mouth cancer. But complementary and alternative medicine treatments may help you cope with mouth cancer and the side effects of cancer treatment, such as fatigue.

Many people with mouth cancer have fatigue during and after treatment. The feeling of being very tired and worn down can continue for years. When combined with care from your healthcare team, complementary and alternative medicine may help relieve fatigue.

Talk with your healthcare team about:

**Gentle exercise**

If you get the OK from your healthcare team, start with gentle exercise. Add more exercise as you feel up to it. Consider walking, swimming, yoga and tai chi.

**Managing stress**

Take control of stress in your daily life. Try stress-reduction techniques such as muscle relaxation or visualization. Writing in a journal also may help.

**Massage therapy**

During a massage, a massage therapist applies pressure to your skin and muscles. Some massage therapists are specially trained to work with people who have cancer. Ask your healthcare team for names of massage therapists in your community.

**Acupuncture**

During an acupuncture session, a trained practitioner inserts thin needles into precise points on your body. Some acupuncturists are specially trained to work with people with cancer. Ask your healthcare team to recommend someone in your community.

**Outlook / Prognosis**

Oral cancer includes cancer in your mouth. Like most forms of cancer, early diagnosis and treatment reduces the chance that oral cancer will spread. Approximately 1/3 of people treated for oral cancer develop new a cancer. If you’ve been treated for oral cancer, talk to your healthcare provider about follow-up examinations.

**Can I spot potential oral cancer?**

Detecting oral cancer early can reduce the chance the cancer will grow or spread. You can detect oral cancer early by doing a monthly self-examination. If you spot changes or something unusual, contact your dentist immediately. Here’s how to examine your mouth, throat and neck for signs of oral cancer:

* Feel your lips, the front of your gums and the roof of your mouth.
* Feel your neck and under your lower jaw for lumps or enlarged lymph nodes.
* Use a bright light and a mirror to look inside your mouth.
* Tilt your head back and look at the roof of your mouth.
* Pull your cheeks out to view the inside of your mouth, the lining of your cheeks and your back gums.
* Pull your tongue out and look at the top, bottom and sides. Gently push your tongue back so you can see the floor of your mouth.

**Living With**

If you’ve been treated for oral cancer, your healthcare provider will share information on how your specific treatment may affect your day-to-day life.

For example, some peoples’ oral cancer is successfully treated by removing the tumor from their lip or mouth. But someone whose oral cancer has spread will have had different and more extensive surgery that may involve reconstructing part of their mouth or jaw.

Regardless of your situation, you may need regular follow-up appointments with your healthcare providers, including your dentist.

**QUESTION AND ANSWERS SET**

What is the difference between pre-cancerous oral cancer and oral cancer?

* Pre-cancerous oral lesions (such as leukoplakia or erythroplakia) are abnormal changes in the cells of the mouth lining that have the potential to develop into cancer but are not yet invasive cancer.
* Oral cancer means malignant cells have invaded beyond the surface and can grow, spread, and damage tissues.
* Pre-cancerous conditions may be *temporary* or reversible with treatment and lifestyle changes, while oral cancer is generally a *chronic* condition requiring active treatment.

What may have caused me to develop cancer?

* Common causes include tobacco use (smoking or chewing), heavy alcohol consumption, human papillomavirus (HPV) infection, chronic irritation, and poor oral hygiene.
* Environmental factors like sun exposure (for lip cancer) and genetic predisposition may also play roles.

What tests will I need, and what do they entail?

* Biopsy: A small tissue sample taken from the lesion to confirm diagnosis.
* Imaging: MRI, CT, or PET scans to determine tumor size, location, and spread to lymph nodes or other organs.
* Physical examination: Thorough inspection of the mouth, throat, and neck.
* Blood tests: To assess overall health and readiness for treatment.

What’s the best course of action?

* The primary treatment is usually surgery to remove the tumor.
* Depending on the stage and location, radiation therapy and/or chemotherapy may be recommended either before or after surgery.
* For early-stage cancers, radiation alone may sometimes suffice.
* Treatment plans are individualized based on tumor size, location, and patient health.

What are the alternatives to the primary approach that you’re suggesting?

* Non-surgical options include radiation therapy alone or combined with chemotherapy (chemoradiation).
* Emerging therapies like targeted therapy, immunotherapy, photodynamic therapy, or electroporation may be options in select cases or clinical trials.
* For patients unable or unwilling to undergo surgery, these alternatives may offer disease control.

If I need surgery, will I need reconstructive surgery?

* Depending on the tumor size and location, reconstructive surgery may be necessary to restore appearance and function (e.g., speech, swallowing).
* Small tumors may require minimal reconstruction, while larger resections might need flaps or grafts.

Should I see a specialist? What will that cost, and will my insurance cover it?

* Yes, seeing a head and neck cancer specialist or multidisciplinary team is strongly recommended for optimal care.
* Costs and insurance coverage vary widely by location and plan; most insurance covers specialist consultations and standard treatments.
* Your healthcare provider or insurance company can provide details on coverage and referrals.

What can I do to ease my symptoms?

* Maintain good oral hygiene.
* Use pain relievers as recommended.
* Avoid irritants like tobacco, alcohol, and spicy foods.
* Stay hydrated and eat soft, nutritious foods.
* Your care team may provide mouth rinses or medications to reduce pain and inflammation.

What lifestyle changes can I make to help with treatment and recovery?

* Quit smoking and avoid alcohol completely.
* Eat a balanced diet rich in fruits and vegetables.
* Practice good oral care to prevent infections.
* Stay physically active as tolerated.
* Attend all follow-up appointments and communicate openly with your healthcare team.

**DIFFERENTIAL DIAGNOSIS**

Precancerous Lesions

* Leukoplakia: White patches that cannot be scraped off, with variable risk of malignant transformation.
* Erythroplakia: Red, velvety patches with a higher risk of progressing to cancer.
* Proliferative verrucous leukoplakia: Aggressive form of leukoplakia with high malignant potential.

Benign Oral Mucosal Lesions

* Geographic tongue: Benign migratory glossitis with irregular red patches.
* Median rhomboid glossitis: Smooth, red, rhomboid-shaped lesion on the tongue dorsum.
* Necrotizing sialometaplasia: Benign inflammatory lesion mimicking malignancy.
* Hairy tongue and oral hairy leukoplakia: Benign conditions often linked to smoking or immunosuppression.
* Oral candidiasis: Fungal infection causing white plaques.
* Herpetic gingivostomatitis and herpes labialis: Viral infections causing painful ulcers or vesicles.
* Aphthous ulcers and traumatic ulcers: Painful, benign ulcerations.

Benign Tumors and Other Lesions

* Papilloma: Benign epithelial tumor often caused by HPV.
* Lipoma: Benign fatty tumor.
* Mucocele and ranula: Mucous cysts arising from salivary glands.
* Neurofibroma and hemangioma: Benign nerve sheath and vascular tumors.
* Oral keratoacanthoma: Rapidly growing benign lesion resembling squamous cell carcinoma.

Malignant Tumors

* Squamous cell carcinoma (SCC): The most common oral cancer, often presenting as ulcers, masses, or leukoplakic/erythroplakic lesions.
* Verrucous carcinoma: A well-differentiated variant of SCC with warty growth.
* Lymphoepithelial carcinoma: Rare, often associated with Epstein-Barr virus.
* Salivary gland malignancies: Mucoepidermoid carcinoma, adenoid cystic carcinoma, etc.
* Melanoma: Rare but aggressive pigmented or non-pigmented tumor.
* Lymphoma: May present as an oral mass or ulcer.
* Metastatic tumors: Secondary cancers from distant primaries involving the oral cavity.

Infectious and Inflammatory Conditions

* Bacterial infections: Can cause ulcers or swelling mimicking cancer.
* Autoimmune diseases: Such as lichen planus or pemphigoid, which may cause mucosal changes.

**EPIDEMIOLOGY**

Incidence and Mortality

* In the United States in 2025, approximately 15,730 new cases of mouth cancer (oral cavity excluding tongue and pharynx) are expected, with about 3,360 deaths.
* Globally, there were about 389,846 new cases of lip and oral cavity cancer in 2022, making it the 16th most common cancer worldwide.
* The global number of deaths from mouth and oral cancer was approximately 188,438 in 2022.
* Mouth and oral cancer incidence and mortality rates tend to be higher in men than women worldwide.
* In the US, the incidence rate is roughly 11.6 per 100,000 persons per year for oral cavity and pharynx cancers combined.

Geographic and Demographic Patterns

* The highest incidence rates are reported in South-Central Asia, Melanesia, Central and Eastern Europe, and parts of Western Europe and Australia/New Zealand.
* Countries with the highest absolute number of cases include India, China, and the United States.
* Incidence rates are higher in populations with low to medium Human Development Index (HDI), often linked to lifestyle and environmental risk factors.
* The disease is most commonly diagnosed in older adults, with incidence peaking in the 70–85+ age group.

Risk Factors Influencing Epidemiology

* Major risk factors include:
* Tobacco use (smoking and smokeless forms)
* Alcohol consumption
* Betel quid chewing, especially prevalent in South and Southeast Asia
* Human papillomavirus (HPV) infection
* Sun exposure (notably for lip cancers)
* Regional differences in risk factor prevalence explain variations in incidence worldwide.

Trends and Projections

* The incidence of oral cavity cancers is rising globally, with projections estimating a 30% increase by 2030.
* Improved early detection and changing risk factor exposure contribute to observed trends, especially in developed countries

**Genetic Mutations and Molecular Features**

* TP53 mutations are the most common and critical genetic alterations in oral cancer, found in approximately 90% of cases in some studies. These mutations disrupt DNA damage repair and cell cycle control, leading to genomic instability, tumor progression, and resistance to chemotherapy and radiotherapy.
* Other important DNA damage repair (DDR) genes frequently mutated include ATR, ATM, CHEK1, and CHEK2. Mutations in these genes impair the cell’s ability to repair DNA damage, contributing to malignancy and therapeutic resistance.
* TERT promoter mutations occur in about 46% of OSCC cases and are linked to tumor cell survival and proliferation. Although their association with clinical features like nodal involvement is unclear, they may serve as prognostic biomarkers.
* Mutations in genes such as HRAS, PIK3CA, NOTCH1, CDKN2A, FBXW7, and BRAF have been identified in oral potentially malignant disorders (OPMDs) like leukoplakia and lichen planus, indicating early molecular changes before cancer develops.
* Novel mutations and genetic variants continue to be discovered through next-generation sequencing (NGS) and whole-exome sequencing (WES), highlighting the heterogeneity of oral cancer genomes and the importance of personalized genomic profiling.
* MicroRNAs (miRNAs), such as miR-1307-5p, miR-24-3p, and others, are differentially expressed in oral cancer and are emerging as potential diagnostic and prognostic biomarkers.
* Mutations affecting angiogenesis-related genes like VEGF-A have been reported, which may influence tumor growth and metastasis.
* Long non-coding RNAs and epigenetic regulators (e.g., NSUN2 variants) also play roles in oral cancer development and progression

**Doctor-Patient Conversation: Mouth Cancer**

Doctor: Hello, thank you for coming in today. I have reviewed your biopsy and imaging results, and I want to discuss your diagnosis and what the next steps are.

Patient: Okay, doctor. What did the tests show?

Doctor: The biopsy confirms that you have mouth cancer, specifically squamous cell carcinoma, which is the most common type. I understand this may be difficult news, and I’m here to help you understand what this means and how we can treat it.

Patient: What kind of cancer is this? How serious is it?

Doctor: Mouth cancer arises from the lining of your oral cavity. The seriousness depends on the size of the tumor, whether it has spread to nearby lymph nodes, and other factors. Based on your scans, your tumor is localized, which is a positive sign.

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, we may also recommend radiation therapy or chemotherapy to reduce the risk of recurrence or treat any microscopic spread.

Patient: What side effects should I expect from treatment?

Doctor: Surgery may cause some pain, swelling, or changes in speech and swallowing, but we have a team to support your recovery. Radiation can cause skin irritation and dryness in your mouth, and chemotherapy may cause fatigue and nausea. We will work closely with you to manage these effects.

Patient: Will I need reconstructive surgery?

Doctor: That depends on how much tissue needs to be removed. For smaller tumors, reconstruction may be minimal or unnecessary. For larger resections, reconstructive surgery helps restore appearance and function.

Patient: How will treatment affect my daily life? Will I be able to work?

Doctor: Many patients continue their daily activities during treatment, though you may need some time off, especially after surgery. We’ll tailor your treatment plan to your lifestyle and support you throughout.

Patient: Should I see a specialist?

Doctor: Yes, I recommend seeing a multidisciplinary head and neck cancer team, including surgeons, oncologists, speech therapists, and nutritionists. This team approach offers the best outcomes.

Patient: What can I do to help myself during treatment?

Doctor: Maintaining good oral hygiene, eating a balanced diet, quitting smoking and alcohol, and following your care team’s advice will help your recovery.

Patient: What happens if I don’t have treatment?

Doctor: Without treatment, the cancer can grow and spread, causing serious complications. Early treatment offers the best chance for cure and preserving quality of life.

Patient: Thank you, doctor. This is a lot to take in, but I appreciate your help.

Doctor: I understand this is overwhelming. Please write down any questions you have, and bring a family member or friend to your next visit if you like. We’re here to support you every step of the way.

REFERENCES

[Oral Cancer: Causes, Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/11184-oral-cancer#outlook-prognosis)

[Mouth cancer - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/mouth-cancer/diagnosis-treatment/drc-20351002)

**Laryngeal cancer**

Laryngeal cancer affects your larynx, part of your throat. Your larynx helps you speak, breathe and swallow. It contains your vocal cords.

[Cancer](https://my.clevelandclinic.org/health/diseases/12194-cancer) affecting your larynx or vocal cords happens when cells grow uncontrollably in your larynx. As these cancerous (malignant) cells multiply, they invade tissues and damage your body.

Laryngeal cancer can form in any of the three main parts of your larynx:

* Supraglottis (upper part): More than one in three laryngeal cancers (35%) start here.
* Glottis (middle part): More than half of laryngeal cancers (60%) start here, where your vocal cords are.
* Subglottis (lower part): About 5% of laryngeal cancers — 1 in 20 — start here.

Laryngeal cancer is part of a group of head and neck cancers. Every year, approximately 12,500 people in the U.S. are diagnosed with laryngeal cancer. About 4,000 people die from it each year.

**Symptoms and Causes**

It’s easy to mistake the first signs of laryngeal cancer for other conditions. The most common symptom — hoarseness that doesn’t improve after a few weeks — is easy to mistake as a sign of a cold. If you experience the following symptoms, talk to a healthcare provider for an accurate diagnosis:

* Sore throat or cough that doesn’t improve.
* Voice changes, such as hoarseness, that don’t improve after two weeks.
* Pain or other difficulties when you swallow.
* Lump in your neck or throat.
* Trouble making voice sounds (dysphonia).
* Ear pain.

If you have these symptoms, seek medical attention right away:

* Trouble breathing (dyspnea).
* Breathing that’s noisy and high-pitched (stridor).
* The feeling that something’s in your throat (globus sensation).
* Coughing up blood (hemoptysis).

**What causes laryngeal cancer?**

Some forms of HPV (human papillomavirus), a sexually transmitted infection (STI), can cause laryngeal cancer.

You also have a much higher chance of developing it if you use tobacco or drink alcohol frequently.

**Risk factors for laryngeal cancer**

Smoking or using other tobacco products greatly increases your risk of developing laryngeal cancer. Drinking alcohol, especially a lot of it (more than one drink daily) also raises your risk. And using alcohol and tobacco together increases your risk even more.

Other risk factors of laryngeal cancer include:

* Age: Laryngeal cancer happens more in people age 55 and older.
* Sex: Men are about five times more likely to develop this cancer, possibly because smoking and heavy alcohol consumption happen more among this group.
* History of head and neck cancer: About 1 in 4 (25%) people who have had head and neck cancer will get it again.
* Job: People exposed to certain substances at work are at higher risk. These substances include sulfuric acid mist, wood dust, nickel, asbestos or manufacturing mustard gas. People who work with machines are also at higher risk of developing cancer in their larynx.

**Diagnosis and Tests**

A healthcare provider will ask you about your symptoms and medical history. They’ll do a physical exam, examining your throat and neck. After the initial exam, you’ll most likely need other tests to confirm a diagnosis.

**What tests help diagnose laryngeal cancer?**

Diagnostic tests include:

* Imaging scans: CT or MRI scans provide detailed images of the inside of your body. They can show a tumor’s size and where it’s located. A chest X-ray can show if cancer has spread to your lungs.
* Laryngoscopy: During a laryngoscopy, a provider uses a thin, lighted tube called an endoscope to examine your larynx.
* PET scan: During a PET scan, a provider injects a small, safe dose of a radioactive substance into your vein. The substance highlights areas with cancer cells.
* Biopsy: During a biopsy, a provider removes a small piece of abnormal tissue from your larynx to examine under a microscope. A specialist called a pathologist will examine the cells and look for certain protein markers. Some types of cancer treatments only work on cancer cells with specific protein markers.

**Stages of laryngeal cancer**

Part of a diagnosis involves staging the cancer. Your care team will figure out how severe the disease is — how far the tumor has grown and if and where it has invaded tissues in your body.

Stages of laryngeal cancer include:

* Early laryngeal cancer: In stages 0, 1 and 2, the tumor is small. Cancer hasn’t spread beyond your larynx.
* Advanced laryngeal cancer: In stages 3 and 4, the tumor has grown larger. It’s affected your vocal cords or invaded your lymph nodes or other areas of your body.

**Where does laryngeal cancer spread first?**

Laryngeal cancer that spreads beyond your larynx may invade your [thyroid](https://my.clevelandclinic.org/health/body/23188-thyroid), windpipe (trachea), esophagus, [tongue](https://my.clevelandclinic.org/health/body/22845-tongue), lungs, liver and bones.

**Management and Treatment**

Treatment for laryngeal cancer includes:

* Radiation therapy: Radiation oncologists deliver high-energy radiation beams to kill cancer cells. The radiation targets only the tumor to minimize damage to surrounding healthy tissue.
* Chemotherapy: Medical oncologists use medications to kill or slow the growth of cancer cells. People often get chemotherapy intravenously (through a vein). Chemo can cause side effects during treatment that a medical oncologist can help you manage.
* Immunotherapy: This treatment uses your immune system, your body’s natural defenses, to help fight cancer. Immunotherapy is also called biologic therapy.
* Targeted therapy: This treatment targets cancer cells with specific types of proteins, preventing the cells from multiplying.
* Surgery: For early laryngeal cancer, surgery can remove the tumor while preserving your larynx (and your ability to speak and swallow). For advanced cancer, surgeons often need to do a laryngectomy, surgery that removes your entire larynx.

You may have more than one treatment. For example, people sometimes have chemotherapy or radiation therapy after surgery to destroy any remaining cancer cells.

**What laryngeal surgery procedures are available?**

Surgery removes cancer. The goal of laryngeal cancer surgery is to remove the tumor while preserving your larynx’s function. The surgeon may need to remove part or all of your larynx. Surgical procedures include:

* Cordectomy: Removes part or all of a vocal cord, usually through your mouth.
* Supraglottic laryngectomy: Removes the supraglottis (the upper part of your larynx), either through your neck or through your mouth.
* Hemilaryngectomy: Removes half of your larynx, preserving your voice.
* Partial laryngectomy: Removes part of your larynx so you retain your ability to talk.
* Total laryngectomy: Removes your entire larynx, through your neck.
* Thyroidectomy: Removes all or part of your thyroid gland.
* Laser surgery: Removes a tumor in a bloodless procedure using a laser beam.

**How does the care team figure out the best treatment for laryngeal cancer?**

For early laryngeal cancer, your care team will likely recommend surgery or radiation therapy. Research has shown that both are effective. Your team will base the decision on several factors, including:

* Which treatment will preserve your ability to speak and swallow.
* Your preferences, wishes and ability to follow the treatment plan.
* Your age.
* Other conditions you may have.
* Demands on your voice, including for your job.
* How your voice sounds.
* If you currently smoke or previously smoked.
* Your ability to breathe.
* Support from your loved ones.

**Outlook / Prognosis**

After your treatment, you’ll continue to have follow-up appointments with your healthcare provider to make sure you’re recovering well. Your provider will:

* Treat any pain.
* Help you manage swallowing problems or mucositis (ulcers in your digestive tract).
* Discuss your diet to make sure you’re eating and swallowing with no problems.
* Prescribe physical therapy for scarring in your neck or trouble opening your mouth.

**What’s the outlook for people with laryngeal cancer?**

Your outlook depends on several factors, such as your cancer’s stage, your age and overall health. Generally, early laryngeal has a better cure rate. Advanced cancer that spreads to other areas has a poorer survival rate.

But even advanced laryngeal cancer can be cured. If it comes back, it usually happens within the first two or three years after treatment. After five years, there’s a very low risk of cancer returning. But if you smoke or have alcohol use disorder and don’t stop using these substances, you’re at higher risk of developing new cancers in this region.

**Will I have a stoma?**

If you have a total laryngectomy, your surgeon will put a new airway in your throat called a stoma. The stoma helps you breathe. It may be permanent or temporary. To take care of your stoma:

* Check it daily to make sure it’s clean and mucus-free.
* Clean mucus from the stoma by coughing it out or using saline spray and cloth.
* Keep it moist with saline spray.
* Clean the stoma area with mild soap and water.
* Don’t submerge the stoma in water.
* Cover the stoma to keep dust out, using a scarf or a special stoma cover. And keep it covered when shaving or in the shower.

**Prevention**

You can’t prevent all cancer. But you can lower your risk for developing cancer, including laryngeal cancer, with healthy behaviors:

* Quit smoking and avoid tobacco products.
* Limit alcohol consumption and get treatment for alcohol use disorder.
* Eat a healthy diet.

**Is there screening for laryngeal cancer?**

There’s no regular screening test for laryngeal cancer. But talk to a healthcare provider if you have hoarseness, other voice changes or a persistent cough. Early detection catches cancer early, when it’s easiest to treat.

**Living With**

If you smoke, it’s important to quit. Don’t smoke before or during treatment and stay tobacco-free even after you finish treatment. People who smoke after treatment have a higher chance of developing another type of cancer. But people who stop smoking have a much lower risk of cancer. Smoking also prevents you from healing completely, and it may worsen treatment side effects.

**Will I be able to use my voice after laryngeal cancer treatment?**

If you had a total laryngectomy (surgeons removed your larynx), you’ll need to learn a new way to speak. A speech therapist can help. If the surgeon only removed part of your larynx, your voice may feel hoarse at first, but you’ll likely regain your voice. Still, it may feel and sound different from before.

Other treatments, like radiotherapy may cause you to lose your voice temporarily, but it usually returns once your larynx has had time to heal.

**What questions should I ask my doctor?**

What stage is the cancer?

* Laryngeal cancer staging depends on tumor size, location (supraglottis, glottis, subglottis), lymph node involvement, and distant spread.
* Early stages (I and II) involve smaller tumors confined to the larynx without lymph node spread.
* Advanced stages (III and IV) involve larger tumors, vocal cord fixation, lymph node involvement, or spread beyond the larynx.
* Your healthcare provider will determine the stage using imaging (CT, MRI, PET) and physical examination.

What are my treatment options?

* Early-stage laryngeal cancer: Often treated with either radiation therapy or surgery (including laser excision), both with good cure rates.
* Locally advanced cancer: Usually treated with a combination of radiation and chemotherapy (concurrent chemoradiation) aiming to preserve the larynx.
* Extensive or bulky tumors: May require total laryngectomy (removal of the entire larynx) sometimes followed by radiation or chemotherapy.
* Targeted therapies and immunotherapies (e.g., cetuximab, pembrolizumab, nivolumab) are used especially in recurrent or metastatic cases or when chemotherapy is unsuitable.

How will treatment affect my speaking, breathing, and swallowing?

* Treatments can affect voice quality, swallowing, and breathing depending on the extent of surgery or radiation.
* Partial laryngectomy or laser surgery may preserve voice and swallowing function.
* Total laryngectomy results in loss of natural voice and breathing through a stoma (neck opening), requiring speech rehabilitation.
* Radiation and chemoradiation can cause temporary swallowing difficulties, dry mouth, and voice changes.

Will I need rehabilitation after treatment?

* Yes, rehabilitation is often necessary, including:
* Speech therapy to regain communication skills.
* Swallowing therapy to address dysphagia.
* Respiratory therapy if breathing is affected.
* Multidisciplinary care teams provide support for functional recovery.

Will the cancer come back?

* Recurrence risk depends on stage and treatment success.
* Most recurrences occur within the first 2–3 years after treatment.
* Regular follow-up and monitoring are essential to detect and manage recurrences early.
* Continued smoking or alcohol use increases risk of recurrence or new cancers.

How can I stay healthy?

* Quit smoking and avoid alcohol to reduce risk of recurrence and new cancers.
* Maintain good nutrition and oral hygiene.
* Attend all follow-up appointments and report new symptoms promptly.
* Engage in rehabilitation and supportive care as recommended.
* Stay physically active as tolerated to improve overall health and recovery

**Who helps diagnose and treat laryngeal cancer?**

A laryngeal cancer care team often consists of multiple providers from different fields:

* Head and neck surgeons are otolaryngologists with specialized training to remove cancers in the head and neck region.
* Radiation oncologists use radiation therapy to treat cancer.
* Medical oncologists use medication, such as chemotherapy, to treat cancer.
* Dentists and oral surgeons offer services such as X-rays and treat oral cancer.
* Speech therapists (speech-language pathologists) evaluate and treat speech, language, voice, cognitive and swallowing disorders.
* Registered dietitians help people find a nutritious diet based on their health, condition, illness or injury.
* Social workers can address concerns and provide information to patients and families. They also offer counseling, referrals to local and national resources, information about support groups and financial assistance information.
* Primary care providers often oversee general medical care during cancer treatment.

**Malignant Tumors to Differentiate From Laryngeal Cancer**

* Mucoepidermoid carcinoma of the larynx: A rare salivary gland malignancy that can be mistaken for squamous cell carcinoma (SCC) or adenosquamous carcinoma. It often presents as a submucosal mass with progressive symptoms but intact mucosa. Histological and immunohistochemical studies (e.g., mucicarmine stain) are essential for differentiation because treatment and prognosis differ from SCC.
* Adenosquamous carcinoma: Another rare malignancy with features overlapping with SCC and mucoepidermoid carcinoma.
* Lymphoma: Can present as a mass in the larynx and mimic cancer symptoms.
* Metastatic tumors: Secondary involvement of the larynx from distant primaries.

Benign and Inflammatory Conditions

* Chronic laryngitis: Inflammation causing hoarseness and swelling, often due to infection or irritants.
* Laryngeal syphilis: Infectious cause with ulcerative or granulomatous lesions.
* Vocal cord polyps, nodules, cysts: Benign lesions causing hoarseness.
* Laryngeal papillomatosis: Benign wart-like growths caused by HPV.
* Laryngeal amyloidosis: Rare deposition disease that can cause mass effect.
* Granulomas: Inflammatory lesions often related to irritation or trauma.

Other Considerations

* Vocal cord paralysis or paresis: Can cause hoarseness but is not a tumor.
* Reflux laryngitis: Inflammation due to acid reflux mimicking cancer symptoms.
* Benign tumors: Such as chondromas or hemangiomas.

**EPIDEMIOLOGY**

The American Cancer Society’s most recent estimates for laryngeal cancer in the United States for 2025 are:

* About 13,020 new cases of laryngeal cancer (10,110 in men and 2,910 in women)
* About 3,910 people (3,140 men and 770 women) will die from laryngeal cancer

About 60% of laryngeal cancers start in the glottis (the area containing the vocal cords), while about 35% develop in the supraglottic area (above the vocal cords). The rest develop in either the subglottis (below the vocal cords) or overlap more than one area so that it is hard to tell where they started.

Most people diagnosed with laryngeal cancer are 55 or older; a very small number of people diagnosed are younger than 55. The average age of people diagnosed with laryngeal cancer is about 66.

Black men are more likely to develop laryngeal cancer than White men and are more likely to die from it. It is also much more common in men than women.

The rate of new cases of laryngeal cancer is falling by about 2% to 3% a year, most likely because fewer people are smoking. Over the past 10 years, the death rate is also dropping about 2% to 3% each year.

**Lifetime chance of getting laryngeal cancer**

Overall, the lifetime risk of developing laryngeal cancer is about 1 in 200 for men and 1 in 840 for women. A number of other factors can also affect your risk for developing laryngeal cancer.

**Doctor-Patient Conversation: Laryngeal Cancer**

Doctor: Hello, thank you for coming in today. I have reviewed your biopsy and imaging results, and I want to talk with you about your diagnosis and treatment options.

Patient: Okay, doctor. What did the tests show?

Doctor: The biopsy confirms that you have laryngeal cancer, which is a malignant tumor in your voice box. Most laryngeal cancers are squamous cell carcinomas. Your scans show that the tumor is localized, which is good news because it means we have several treatment options.

Patient: What stage is my cancer? Has it spread?

Doctor: Based on the imaging and examination, your cancer is at an early stage and has not spread to lymph nodes or other parts of your body. We will continue to monitor closely, but this means we can focus on treatments that aim to cure while preserving your voice and swallowing functions.

Patient: What are my treatment options?

Doctor: For early-stage laryngeal cancer, we typically recommend either surgery or radiation therapy. Surgery can sometimes be done with minimally invasive techniques that preserve your voice. Radiation therapy is another option that can also preserve the larynx. For more advanced stages, combined treatments including chemotherapy might be necessary.

Patient: How will treatment affect my speaking, breathing, and swallowing?

Doctor: Treatments can affect these functions to varying degrees. Surgery or radiation may cause temporary hoarseness, swallowing difficulties, or throat discomfort. In cases where the entire larynx needs to be removed, you will breathe through a stoma in your neck and will need speech rehabilitation. But many patients retain good function, especially with early treatment.

Patient: Will I need rehabilitation after treatment?

Doctor: Yes, rehabilitation is important. Speech-language pathologists will work with you on voice therapy and swallowing exercises. If you have a total laryngectomy, specialized voice rehabilitation, such as using an electrolarynx or tracheoesophageal puncture (TEP), will be provided.

Patient: What are the chances the cancer will come back?

Doctor: Recurrence risk depends on the stage and treatment success. Early-stage cancers treated appropriately have a good chance of cure. We will schedule regular follow-ups with exams and imaging to detect any recurrence early.

Patient: How can I stay healthy during and after treatment?

Doctor: Quitting smoking and avoiding alcohol are the most important steps you can take. Maintaining good nutrition, oral hygiene, and attending all follow-up appointments will help your recovery. Physical activity as tolerated is also beneficial.

Patient: Will treatment affect my daily life and work?

Doctor: Many patients continue their daily activities during treatment, though some may need time off, especially after surgery. We will tailor your treatment plan to your lifestyle and support you throughout.

Patient: Are there resources or support groups I can access?

Doctor: Absolutely. We can connect you with specialist nurses, speech therapists, and support groups. Organizations like Cancer Research UK and the American Cancer Society also provide helpful information and counseling services.

Patient: Thank you, doctor. This helps me understand what to expect.

Doctor: You’re welcome. Please write down any questions you have, and feel free to bring a family member or friend to your next appointment. We’re here to support you every step of the way.

**REFERENCES**

https://www.cancer.org/cancer/types/laryngeal-and-hypopharyngeal-cancer/about/key-statistics.html

[Laryngeal Cancer: Symptoms, Causes & Treatment](https://my.clevelandclinic.org/health/diseases/16611-laryngeal-cancer#overview)

**ANAL CANCER**

**DEFINITION AND DESCRIPTION**

Anal cancer is a growth of cells that starts in the anal canal. The anal canal is a short tube at the end of rectum. Stool passes through the anal canal as it leaves the body.

Anal cancer can cause symptoms such as rectal bleeding, blood in the stool and anal pain. As it grows, it might cause a growth or lump. Sometimes these symptoms might be mistaken for hemorrhoids.

In the past, most people with anal cancer had surgery to remove the cancer. Often this operation involved making a new way for waste to leave the body. Today, most anal cancer treatment involves chemotherapy and radiation therapy. With this approach, surgery might not be needed.

**Causes**

Anal cancer happens when cells in the anal canal develop changes in their DNA. A cell's DNA holds the instructions 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 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 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.

Most anal cancers are thought to be caused by human papillomavirus, also called 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.

**Risk factors**

Things that may increase the risk of anal cancer include:

* **Being exposed to human papillomavirus, also called HPV.** HPV is a common virus that's passed through sexual contact. For most people, it causes no problems and goes away on its own. For others, it causes changes in the cells that can lead to many types of cancer, including anal cancer.
* **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 acquiring HPV.
* **Having anal sex.** People who have receptive anal sex have an increased risk of anal cancer.
* **Smoking cigarettes.** People who smoke cigarettes have an increased risk of anal cancer.
* **Having a history of cancer.** Those who have had cervical, vulvar or vaginal cancer have an increased risk of anal cancer.
* **Having a weak immune system.** If the body's germ-fighting immune system is weakened by medicines or illness, there might be a higher risk of anal cancer. People with a weakened immune system include those taking medicines to control the immune system, such as after an organ transplant. Certain medical conditions, such as infection with HIV, also can weaken the immune system.

**Symptoms**

Anal cancer signs and symptoms include:

* Bleeding from the anus or rectum.
* Blood in the stool.
* Pain in the area of the anus.
* A mass or growth in the anal canal.
* Anal itching.
* Having to go to the bathroom more often.

**When to see a doctor**

Make an appointment with a doctor or other healthcare professional if you have any symptoms that worry you.

**Diagnosis**

Tests and procedures used to diagnose anal cancer include:

Examining the anal canal and rectum

During a digital rectal exam, a healthcare professional inserts a gloved, lubricated finger into your anus. The health professional feels the anal canal and rectum for growths or other signs of cancer.

Using a scope to examine the anal canal, called an anoscopy

During an anoscopy, a healthcare professional inserts a thin, flexible tube with a light through the anal canal and rectum. This tube is called an anoscope. A lens on the anoscope allows a healthcare professional to examine the inside of the anal canal.

Imaging tests

Imaging tests make pictures of the body. They can show the location and size of the cancer. Tests might include ultrasound, X-ray, MRI, CT scan and positron emission tomography scan, which also is called a PET scan.

Removing a sample of tissue for testing, also called biopsy

A biopsy is a procedure to remove a sample of tissue for testing in a lab. The sample is often collected during an anoscopy. Special tools can go through the anoscope to collect the cells. 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.

**Staging**

If you're diagnosed with anal cancer, 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, also 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 results of your cancer staging tests to help create your treatment plan.

The stages of anal cancer range from 1 to 4. The lowest number means that the cancer is small and only in the anal canal. A higher stage means the cancer is more advanced. A stage 4 anal cancer has spread to other areas of the body.

**Anal cancer staging**

Healthcare providers use cancer staging systems to plan treatment and set prognoses, or what you can expect to happen after treatment. They consider factors like tumor size, if there’s cancer in your lymph nodes and whether the tumor has spread or metastasized. There are five stages of anal cancer:

Stage 0

There are abnormal cells in your anus’ mucosa, which is the innermost lining of your anus. The abnormal cells aren’t cancerous but may become cancerous. Stage 0 anal cancer is also called high-grade squamous intraepithelial lesion (HSIL).

Stage I

Cancer cells have formed a tumor that measures 2 centimeters or less, or about the size of a peanut.

Stage II

Stage II anal cancer is divided into two stages:

* Stage IIA means there’s a tumor that’s larger than 2 centimeters but smaller than 5 centimeters.
* Stage IIB means that a tumor is 5 centimeters — about the size of a lime — but hasn’t spread from your anus.

Stage III

Stage III is divided into three stages:

* Stage IIIA, when a tumor is 5 centimeters or smaller and has spread to lymph nodes in your anus or groin.
* Stage IIIB, when anal cancer spreads to nearby organs like your [vagina](https://my.clevelandclinic.org/health/body/22469-vagina), urethra or bladder.
* Stage IIIC, when there’s cancer in nearby organs and it’s spread to lymph nodes near your anus or groin.

Stage IV

There’s cancer in your lymph nodes that are far away from your anus and in distant organs like your lungs or your liver.

**Management and Treatment**

Anal cancer treatment depends on the type and cancer stage, but may include:

Radiation therapy

Providers treat anal cancer with external beam radiation therapy (EBRT). Types of EBRT include:

* Intensity-modulated radiation therapy (IMRT), which sends multiple energy beams of different strengths to a tumor.
* Stereotactic body radiation therapy (SBRT), which targets small tumors without damaging nearby healthy tissue.
* Three-dimensional conformal radiation therapy (3D-CRT) that creates a three-dimensional picture of tumors.
* Brachytherapy, which is internal radiation therapy.

Chemotherapy

Healthcare providers often combine chemotherapy and radiation therapy as initial anal cancer treatment. The combined treatments often eliminate anal cancer, so you don’t need surgery.

If you do need surgery, you may have chemotherapy beforehand to shrink the tumor (neoadjuvant chemotherapy) or after surgery to kill any remaining cancer cells (adjuvant chemotherapy).

Surgery

Laparoscopic abdominoperineal resection is a minimally invasive surgery used to treat anal cancer that comes back (recurs) or didn’t respond to radiation therapy and/or chemotherapy. It involves removing your anus, rectum and colon.

If you have this surgery, your surgeon will also do a permanent colostomy so you can eliminate poop into a bag or pouch attached to your body.

Immunotherapy

If you have late-stage anal cancer, your provider may recommend immunotherapy to help you manage your symptoms. Immunotherapy helps your body fight cancer.

**Treatment side effects**

Most cancer treatments may cause side effects. For example, chemotherapy and radiation therapy side effects may include skin irritation, pain in your anal area, fatigue, chemotherapy brain fog, nausea and vomiting.

**Treatment complications**

Healthcare providers may treat anal cancer with surgery. Surgery complications may include:

* A reaction to anesthesia.
* Excessive bleeding.
* Infection.

**Outlook / Prognosis**

**What are anal cancer survival rates?**

Anal cancer survival rates are estimates of the percentage of people with the condition who were alive five years after diagnosis. Rates vary depending on whether a provider diagnoses and treats the condition before it spreads. Overall, 70% of people with anal cancer were alive five years after diagnosis, according to the National Cancer Institute (U.S.). Survival rates by cancer location include:

| **Cancer Stage** | **Survival Rate** |
| --- | --- |
| Stages I and II | 83% |
| Stage III | 67% |
| Stage IV | 36% |

It’s important to remember that survival rates are based on the experiences of large groups of people who may have different health issues. What’s true for them may not be true for you. If you have questions, ask your provider to explain what you can expect.

**Complications**

Anal cancer rarely spreads to other parts of the body. Only a small percentage of cancers are found to have spread. Those that do are especially difficult to treat. Anal cancer that spreads most commonly goes to the liver and the lungs.

**Prevention**

**Take steps to reduce your risk**

There is no sure way to prevent anal cancer. To reduce your risk of anal cancer:

* **Practice safer sex.** Reduce your risk of anal 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.
* **Consider the HPV vaccine.** Receiving a vaccination to prevent HPV infection may reduce your risk of anal cancer and other HPV-related cancers. Ask your healthcare team if an HPV vaccine is right for you.
* **Don't use tobacco.** If you don't use tobacco, don't start. If you currently use tobacco of any kind, talk with a healthcare professional about strategies to help you quit.

**Ask about anal cancer screening**

Screening tests can help detect anal cancer and precancerous cells that may one day develop into anal cancer. Healthcare professionals sometimes recommend screening for people with a high risk of anal cancer.

You might have a high risk of anal cancer if you:

* Have HIV.
* Are taking medicine to control your immune system after an organ transplant.
* Have been diagnosed with precancerous cells in the penis, scrotum, cervix, vagina or vulva.

Screening tests might include:

* **Anal Pap test.** During an anal Pap test, a healthcare professional swabs cells from your anal canal. The cells are tested in a lab to check for cancer cells and cells that look like they could become cancerous.
* **Anal HPV test.** The anal HPV test involves testing cells from the anal canal for infection with HPV.
* **Digital rectal exam.** During a digital rectal exam, a healthcare professional inserts a gloved, lubricated finger into the anus. The health professional feels the anal canal and rectum for growths or other signs of cancer.

Medical groups don't agree on who should have anal cancer screening and what tests should be used. Screening can detect anal cancer when it's small and easier to treat. But studies haven't proved that anal cancer screening can save lives. Talk about the benefits and risks of screening with your healthcare team.

**Alternative medicine**

Alternative medicine treatments won't kill cancer cells. But some alternative medicine treatments may help you cope with the side effects of cancer treatment. Your healthcare team can treat many side effects, but sometimes medicines aren't enough. Alternative treatments may offer additional comfort.

Options for common side effects include the following:

* **Anxiety** — massage, meditation, hypnosis, music therapy, exercise or relaxation techniques.
* **Fatigue** — gentle exercise or tai chi.
* **Nausea** — acupuncture, hypnosis or music therapy.
* **Pain** — acupuncture, massage, music therapy or hypnosis.
* **Sleep problems** — yoga or relaxation techniques.

While these options are generally safe, talk with your healthcare team first to be sure that alternative medicine options won't affect your cancer treatment.

**What questions should I ask my healthcare provider?**

**What’s the difference between anal cancer and anal dysplasia?**

The difference is anal dysplasia isn’t cancer, but it may pave the way for anal cancer. In anal dysplasia, cells in your anus become abnormal. Over time, these abnormal cells could start multiplying, creating cancerous tumors.

**How is anal cancer different from rectal cancer and colon cancer?**

Your anus, rectum and colon are all parts of your digestive system. But the cells that make up each parts’ tissue are very different, which means healthcare providers treat these cancers in different ways.

**Diagnostic Considerations**

Referral to a colorectal surgeon or other advanced practitioner in the field, such as a surgical oncologist familiar with the disease process, is critical to prevent delay in diagnosis and treatment when anal cancer is suspected or diagnosed. An oncologist or specialist oncologist who has interest in digestive cancers or squamous cell carcinoma should be involved early in the diagnostic process to help guide the workup and treatment scheme.

**Differential Diagnoses**

* AIDS anal ulcer
* Anal Fissure
* Anal Fistulas and Fissures
* Chancroid
* DELETE - Condyloma Acuminatum (Genital Warts)
* Extramammary Paget Disease
* Hemorrhoids
* Pruritus ani
* Psoriasis

**Epidemiology**

A study of trends in squamous cell carcinoma of the anus (SCCA), using the US Cancer Statistics dataset, found that in 2001-2015 the incidence of SCCA rose 2.7% annually, with pronounced increases in persons aged 50 years and older. The incidence of distant-stage SCCA tripled over that period, and that of regional-stage SCCA nearly doubled. From 2001-2016, anal cancer mortality rates increased 3.1% per year, with statistically significant increases in those aged 50 years and older.

According to Surveillance, Epidemiology and End Results (SEER) data, the annual age-adjusted rates for new anal cancer cases rose on average 2.2% each year over 2013–2022, while age-adjusted death rates rose on average 4.1% each year over 2014–2023. According to SEER data, the annual rate of new anal cancer cases is 2.0 per 100,000 population and the lifetime risk of developing anal cancer is 0.2%. The American Cancer Society estimates that about 10,930 new cases of anal cancer (7370 in women and 3560 in men) will be diagnosed in 2025, and 2030 deaths will occur (1250 in women and 780 in men).

Risk factors for anal cancer include any of the following:

* Active HPV infection
* Smoking
* Men having sex with men (MSM)
* Anoreceptive sex
* Immunosuppression, with a correlation with low T-cell counts
* HIV infection
* Solid organ transplantation, especially in females ≥10 years after transplantation
* HPV‐related gynecologic precancerous lesions or cancer (vulvar, cervical, or vaginal)

Combinations of two or more factors pose particular risk. For example, a meta-analysis found that the highest incidence of anal cancer was in HIV-positive MSM aged 60 years or older; in this group, the incidence rate was 107.5 per 100,000 person-years.However, although elderly women are not generally considered to be at high risk, a review of SEER data on anal cancer from 2017 to 2021 found that the fastest rate of rise was in White women over age 65 years, with new cases increasing by 4.3% annually during that period, reaching 11.4 cases per 100,000 in 2021. The second highest rate of rise was in Hispanic women over age 65, who showed an annual increase of 1.7%, reaching 7.5 cases per 100,000 people in 2021.

Worldwide, HPV-related cancers account for approximately 4.8% of cancers and 14-15% in less-developed areas such as India and sub-Saharan Africa. HPV infection is a worldwide public health concern that is growing in importance.This highlights the potential benefit of HPV vaccination. A nationwide Danish study found that in women who received at least one dose of HPV vaccine before age 17 years, the risk of high‐grade anal squamous intraepithelial lesions and anal cancer was reduced by 70%, compared with unvaccinated women.

Cancer types other than squamous cell carcinoma are varied and account for only a minority of anal cancers—approximately 20%.The epidemiology of non–squamous cell cancers of the anus (eg, melanoma, adenocarcinoma) tends to correlate more closely to those histologic entities at other body sites.

**Prevention recommendations for anal cancer prevention include the following**:

* Use history, physical examination, and laboratory testing to identify patients at increased risk for anal squamous neoplasms (eg, HIV-positive individuals, men who have sex with men [MSM], women with a history of cervical dysplasia). (Strong recommendation based on moderate-quality evidence, 1B)
* Provide regular follow-up of patients with anal dysplasia, with history, physical examination, and discussion of screening options. (Weak recommendation based on moderate-quality evidence, 2B)
* Consider screening high-risk patients with anal cytology (or anal Papanicolaou tests [Pap smears]); HPV testing may be used as an adjunct. (Weak recommendations based on moderate-quality evidence, 2B)
* High-resolution anoscopy may be considered as a screening option for high-risk patients, when performed by appropriately trained clinicians. (Weak recommendation based on moderate-quality evidence, 2B)
* Topical imiquimod, fluorouracil, trichloroacetic acid, or cidofovir, with close long-term follow-up, are options for the treatment of low-grade or high-grade squamous intraepithelial lesions. (Weak recommendation based on moderate-quality evidence, 2B)
* Vaccination against human papillomavirus (HPV) in men and women under age 26 years for primary prevention is typically recommended; Vaccination of individuals with anal dysplasia for secondary prevention of dysplasia and cancer is not recommended. (Weak recommendation based on high-quality evidence, 2A)
* Patients who have been treated for anal dysplasia may be observed without regular cytology, HPV testing, or anoscopy; however, treatment of visible or palpable disease should be offered. (Weak recommendation based on low or very low-quality evidence, 2C)

Pretreatment evaluation

For the pretreatment evaluation, the ASCRS recommends performing the following:

* A disease-specific history and physical examination, emphasizing symptoms, risk factors, and signs of advanced disease (strong recommendation based on low-quality evidence, 1C)
* Endoscopic and radiologic evaluation, to help determine staging, and assess for metastatic disease (strong recommendation based on low-quality evidence, 1C)
* 2-(18F) fluoro-2-deoxy-D-glucose positron emission tomography (PET)/computed tomography (CT) may be considered as an adjunct radiologic study in the staging of anal SCCs, but does not replace CT scanning for clinical staging (strong recommendation based on low-quality evidence, 1C)

**Treatment recommendations for treatment include the following:**

* For all squamous cell carcinomas (SCCs) of the anal canal, and for most perianal SCCs, combined chemotherapy and radiation therapy is the primary treatment; chemoradiation therapy provides better locoregional control than radiotherapy alone (strong recommendation based on high-quality evidence, 1A).
* For the chemotherapy arm, mitomycin plus 5-fluorouracil (5-FU) is the first-line regimen for anal SCCs (strong recommendation based on high-quality evidence, 1A).
* Radiotherapy doses > 59 Gy provide no oncologic benefit (strong recommendation based on moderate-quality evidence, IB).
* Missed treatments should be avoided, because they are strongly associated with inferior disease control (Strong recommendation based on moderate-quality evidence, IB).
* Abdominoperineal resection is effective salvage therapy for persistent or recurrent disease (strong recommendation based on moderate-quality evidence, 1B).
* Consider systemic chemotherapy in pa­tients with distant metastasis. Metastasectomy, radiation, and radiofrequency ablation can be considered in selected cases (weak recommendation based on low- or very-low–quality evidence, 2C).

Additional treatment recommendations include the following:

* Perianal squamous cancers that are well-differentiated, node-negative, T1 lesions can be adequately treated with wide local excision with 1-cm margins of resection (strong recommendation based on low-quality evidence, IC)
* Patients with HIV or AIDS who present with anal cancer as the first manifestation of their immunosuppression, and who are not medically deconditioned, can be safely treated according to the same regimens as immunocompetent patients (strong rec-ommendation based on medium-quality evidence, IC).

Post-treatment surveillance

The ASCRS recommends that patients treated for anal cancer receive follow-up involving digital rectal examination, anoscopy, and imaging. Surveillance should typically start 8 to 12 weeks from the completion of chemoradiotherapy and should be continued for 5 years (strong recommendation based on moderate-quality evidence, 1B).

Workup, treatment, and post-treatment surveillance of anal carcinoma.

Workup

When biopsy confirms SCC of the anal canal or anal margin, the NCCN recommends the following workup:

* Digital rectal examination (DRE)
* Inguinal lymph node evaluation – Consider biopsy or fine needle aspiration (FNA) of suspicious nodes
* Chest/abdominal CT plus pelvic CT or MRI – Consider PET/CT scan
* Anoscopy
* Consider HIV testing + CD4 level if indicated
* Gynecologic exam for women, including screening for cervical cancer

Treatment

For primary treatment of locoregional SCC of the anal canal, preferred chemoradiation regimens include the following;

* Mitomycin/5-fluorouracil (5-FU) plus radiation therapy (RT)
* Mitomycin/capecitabine plus RT

For RT, the NCCN panel consensus was that intensity-modulated radiation therapy (IMRT) is preferred over 3-D conformal RT. Stereotactic body RT (SBRT) may be considered for patients with oligometastatic disease.

For metastatic SCC of the anal canal, the NCCN recommends primary treatment with 5-FU/cisplatin or carboplatin/paclitaxel, or enrolling the patient in a clinical trial.

For primary treatment of SCC of the anal margin, treatment recommendations vary by clinical stage, as follows:

* T1, N0, well differentiated – Local excision; if margins are adequate, observe; if margins are inadequate, treat with re-excision (preferred) or consider local RT with or without chemotherapy
* T1, N0, poorly differentiated; T2-T4, N0; or any T, N+ – Chemoradiation therapy
* Metastatic disease – Chemotherapy, with or without RT, or clinical trial

Follow-up

The NCCN recommends evaluation in 8-12 weeks with physical examination plus DRE. For patients in complete remission, surveillance recommendations are as follows:

* DRE and inguinal node palpation every 3-6 mo for 5 y
* Anoscopy every 6-12 mo for 3 y
* For patients with T3-T4 disease or positive inguinal nodes – Chest/abdomen/pelvic CT with contrast annually for 3 y

If surveillance reveals recurrent disease, treatment recommendations are as follows:

* Local recurrence – Abdominopelvic resection (APR), plus groin resection if inguinal nodes are positive
* Inguinal node recurrence – Groin dissection; consider RT if patient had no prior groin RT, with or without 5-FU or mitomycin/capecitabine
* Distant metastasis – 5-FU/cisplatin or clinical trial

Surveillance after treatment for local recurrence includes the following:

* Inguinal node palpation every 3-6 mo for 5 y
* Chest/abdomen/pelvic CT with contrast annually for 3 y

Surveillance after treatment for inguinal node recurrence includes the following:

* DRE and inguinal node palpation every 3-6 mo for 5 y
* Anoscopy every 6-12 mo for 3 y
* Chest/abdomen/pelvic CT with contrast annually for 3 y

If initial post-treatment evaluation reveals persistent disease, the NCCN recommends re-evaluation in 4 wk; if serial exams show regression or stable disease, the NCCN recommends continued observation, re-evaluation in 3 mo, and biopsy at 6 mo. In cases of progressive disease, biopsy proven, recommendations are as follows:

* Locally recurrent – APR, plus groin resection if inguinal nodes are positive
* Metastatic disease – 5-FU/cisplatin or clinical trial

Diagnosis, treatment, and follow-up of anal cancer.

Diagnosis

ESMO recommendations for diagnosis of anal cancer include the following:

* Digital anorectal examination (DRE) is essential for detection of lesions in the anal area.
* Biopsy is mandatory to confirm squamous cell carcinoma of the anus (SCCA)
* All suspicious anal lesions should be excised or biopsied. Targeted biopsy of anal lesions suspicious for anal intraepithelial neoplasia (AIN) is mandatory in high-risk groups to exclude invasive disease.
* Female patients with AIN should be screened for synchronous cervical, vulvar, and vaginal intraepithelial neoplasia.
* Consider HIV testing in patients with recurrent or multifocal AIN.
* High-resolution T2-weighted MRI is needed for optimal assessment of primary tumour and lymph nodes.
* Magnetic resonance imaging (MRI) may also be helpful to note the relationship of tumor/nodes to the sacral segment levels, which would also assist in RT planning.
* Lymph nodes can be difficult to interpret on MRI. Generally, they are more likely to be malignant if they exhibit mixed signal intensity and if breach of the lymph node capsule by tumor signal intensity is observed on high-resolution T2-weighted MRI.
* Contrast-enhanced computed tomography (CT) scanning of the thorax, abdomen, and pelvis is a requirement for all patients to assess potential metastatic disease sites at diagnosis and follow-up.
* Further characterization of enlarged inguinal nodes by ultrasound-guided fine needle aspiration may be helpful when confirmatory features of malignancy are not evident on either MRI or positron emission tomography/CT (PET-CT).
* PET-CT may be considered for staging and assist in RT planning.
* Assessment of human papillomavirus (HPV) or p16 status may be considered, as the results can help predict treatment response.

Treatment

Recommendations for primary treatment include the following:

* Radiation therapy (RT) with concomitant 5-fluorouracil (5-FU) and mitomycin C is recommended as standard of care for patients with localized SCCA. Capecitabine can be possibly used as an alternative to 5-FU.
* Chemoradiotherapy (CRT) for locally advanced anal cancer should be given with an RT dose of > 50 Gy; the optimal dose for different tumor stages is not known.
* Neoadjuvant or adjuvant chemotherapy is generally not recommended.
* Elderly patients who can tolerate treatment should be treated with curative CRT. Patients who cannot tolerate CRT may benefit from RT for local control.
* Intensity-modulated RT (IMRT), volumetric modulated arc therapy (VMAT), or 3D conformal RT are the recommended RT techniques, with RT dose constraints to normal tissue.
* The optimal RT dose for primary anal cancer is not known, but doses of at least >45-50 Gy are recommended for T1-2N0 tumors, and doses of 50.4 Gy or higher for T3-4 or N1 tumors.

Recommendations for treatment of anal margin cancers include the following:

* Early anal margin cancers (cT1N0M0) can be treated definitively by local excision, with the goal of achieving histologic clearance of > 1 mm without damage to the anal sphincter muscle.
* CRT is recommended for anal margin cancers (T1N0M0) if the margin is ≤1 mm.

Recommendations for locally recurrent or residual disease include the following:

* Patients with locally residual or recurrent disease after CRT should be considered for salvage surgery.
* Residual or recurrent tumors may be considered for histologic confirmation.
* For patients with locally recurrent disease, MRI in conjunction with specialist multidisciplinary team assessment is important to optimize surgical cure].
* Involvement of the anal sphincter complex requires exenterative surgery, and imaging assessment should include a thorough assessment of the pelvic compartments to enable surgical planning (beyond total mesorectal excision).
* The mainstay of salvage surgery is abdomino-perineal excision, but more radical exenterative operations can be considered to achieve an R0 resection. APE for relapsed anal cancer is a different operation from that used for rectal cancer; perineal plastic reconstruction with musculo-cutaneous flaps should be considered in almost all cases.

Recommendations for advanced anal cancer in chemotherapy-naive patients include the following:

* Carboplatin plus paclitaxel should be considered a new standard of care.
* Cisplatin/5-FU/capecitabine, carboplatin, or docetaxel-based combinations are alternatives.
* Programmed cell death ligand 1 (PD-L1) inhibitors may be considered in patients whose disease has progressed on first-line therapy in clinical trials.

**QUESTION AND ANSWER SET**

What kind of anal cancer do I have?

Anal cancer is most commonly squamous cell carcinoma, but other types include adenocarcinoma, melanoma, and small-cell carcinoma. Your biopsy will specify the type, which influences treatment options and prognosis.

2. What is the grade and stage of my cancer?

The grade describes how abnormal the cancer cells look under a microscope (low to high grade). The stage indicates the size of the tumor and whether it has spread to lymph nodes or other organs. Staging is done with imaging and physical exams.

3. Has the cancer spread anywhere else in my body?

Imaging tests such as CT, MRI, or PET scans help determine if the cancer has spread to lymph nodes or distant organs like the lungs or liver.

4. What are my treatment choices?

Treatment usually involves chemoradiation (combined chemotherapy and radiation), which is effective for most stages I-III. Surgery is reserved for persistent or recurrent disease. Chemotherapy alone or targeted therapies may be options in advanced cases.

5. What treatment do you think is best for me?

Your care team will recommend treatment based on your cancer’s type, stage, and your overall health. Chemoradiation is standard for most, but clinical trials or alternative approaches may be considered.

6. Will I need a colostomy?

Most patients do not need a permanent colostomy. However, if surgery is required for advanced or recurrent cancer, a colostomy might be necessary.

7. How will treatment affect my daily life?

Side effects from radiation and chemotherapy can include fatigue, skin irritation, diarrhea, pain during bowel movements, and sexual dysfunction. These often improve after treatment but may require supportive care.

8. What are the success rates and prognosis?

Early-stage anal cancer treated with chemoradiation has a high cure rate (around 80-90%). Prognosis worsens with advanced disease or metastasis.

9. Are there clinical trials I should consider?

Clinical trials may offer access to new treatments and are worth discussing with your oncologist.

10. What tests will I need during and after treatment?

Regular follow-up includes physical exams, anoscopy, and imaging every 3-6 months for the first 2 years, then less frequently. Monitoring helps detect recurrence early.

11. How can I manage symptoms and side effects?

Good skin care during radiation, pain management, nutritional support, and counseling can help. Support groups and peer programs are available.

12. Will my insurance cover treatment?

Coverage varies; your healthcare team or social workers can help navigate insurance and financial assistance

**Genomic Alterations in Anal Cancer**

* PIK3CA mutations are the most frequent genetic alteration, present in approximately 30% or more of anal cancers. These mutations often involve well-known oncogenic hotspots such as E542K and E545K and lead to activation of the PI3K pathway, promoting tumor growth. PIK3CA mutations represent actionable targets, with PI3K inhibitors like alpelisib approved in other cancers and under investigation in anal cancer.
* TP53 mutations are primarily found in HPV-negative anal cancers, while HPV-positive tumors typically retain wild-type TP53 but show p16 overexpression. TP53 mutations contribute to genomic instability and poorer prognosis.
* Other recurrent mutations include FBXW7, PTEN, NRAS, ATM, KMT2C, KMT2D, RB1, FAT4, NF1, CDKN2A, CTNNB1, and ARID1A, many of which are involved in cell cycle regulation, DNA repair, and chromatin remodeling.
* Anal cancer shows a mutational burden similar to head and neck squamous cell carcinoma (HNSCC), consistent with shared HPV-associated oncogenesis.
* HPV infection (especially HPV16) is a major etiologic factor, with HPV-positive tumors displaying distinct molecular profiles, including high p16 expression and immune checkpoint molecule expression such as PD-L1, which has implications for immunotherapy.
* Mutational heterogeneity is observed between pre-treatment tumor tissue and post-treatment circulating tumor DNA (ctDNA), indicating tumor evolution and potential emergence of new actionable mutations during therapy

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**Adrenocortical carcinoma**

Adrenocortical carcinoma is cancer in your adrenal cortex, the outer layer of your adrenal glands. These glands are on top of your kidneys and produce hormones that, among other things, manage your body’s metabolism, blood pressure and how you react to stress.

In adrenocortical carcinoma, there are cancerous tumors on your adrenal glands that may release abnormally large amounts of hormones. The flood of hormones may affect how your body works. Fast-growing tumors may press on nearby organs. In some instances, healthcare providers can treat adrenocortical carcinoma, but the condition often comes back (recurs).

This condition typically affects adults, but children sometimes develop it, too. This article focuses on adrenocortical carcinoma in adults.

**Types of adrenocortical carcinoma**

There are two types — functioning and non-functioning — that cause different symptoms:

* Functioning tumors: Most adrenocortical carcinomas are functioning. They release excessive amounts of hormones, including aldosterone, cortisol, estrogen and testosterone. Symptoms vary depending on the type of hormone.
* Non-functioning tumors: These tumors don’t affect hormone production, but they can grow so large that they press on nearby organs and tissues.

Adrenocortical carcinoma is very rare even, though it’s the most common type of adrenal cancer. Each year, about 1 in 1 million people receive a diagnosis of adrenocortical carcinoma.

**Symptoms and Causes**

You can have this condition without having symptoms. Studies show that 20% to 30% of adrenocortical carcinoma diagnoses happen after healthcare providers do imaging tests for unrelated health issues. When adrenocortical carcinoma symptoms develop, they may include:

* Abdominal (belly) pain.
* Hirsutism (excess body or facial hair in females).
* Gynecomastia (enlarged male breasts).
* High blood pressure.
* High blood sugar.
* Weight gain in your face, neck and trunk.

**How aggressive is adrenocortical carcinoma?**

It’s very aggressive because the tumors can grow very quickly and spread (metastasize) from your adrenal gland to other areas of your body, including your lungs or bones.

**What causes adrenocortical carcinoma?**

Researchers don’t know the exact cause. Some people develop adrenocortical carcinoma because they have inherited conditions that increase the risk that they’ll develop the condition.

In other cases, certain genetic mutations (changes) appear to increase risk. For example, research shows changes in the tumor suppressor genes *TP53* and *IGF2* appear to drive adrenocortical carcinoma. Tumor suppressor genes manage cell growth. When these genes change, your cells may multiply uncontrollably and become cancerous tumors.

**What inherited conditions increase my risk?**

Having any of the following conditions increases your risk of developing adrenocortical carcinoma:

* Beckwith-Wiedemann syndrome.
* Carney complex.
* Familial adenomatous polyposis (FAP).
* Li-Fraumeni syndrome.
* Lynch syndrome.
* Multiple endocrine neoplasia (MEN1).
* Neurofibromatosis Type 1 (NF1).
* Von Hippel-Lindau (VHL) syndrome.

**Complications of adrenocortical carcinoma**

It can spread (metastasize) very quickly. Cancer that spreads from your adrenal gland to other areas of your body is more difficult to treat. Tumors that release certain hormones may cause conditions including:

* Cushing syndrome: This condition happens when adrenal glands release too much cortisol.
* Conn’s syndrome: Excess aldosterone causes this condition.

**Diagnosis and Tests**

If tests for other issues reveal a tumor on your adrenal gland or you have certain symptoms, your healthcare provider will do the following:

* Imaging tests, such as MRI, CT scan or PET scan to look for tumors.
* Blood tests and urinalysis to check hormone levels.

Your provider may do a biopsy to confirm that a tumor is cancerous, as well as obtain tissue samples.

**Stages of adrenocortical carcinoma**

Healthcare providers use cancer staging systems to plan treatment and develop a prognosis (what you can expect to happen after treatment). They establish adrenocortical carcinoma stages by evaluating tumor size and location and whether the tumor has spread to nearby lymph nodes or other more distant organs. Adrenocortical carcinoma stages include:

* Stage I: The tumor is 5 centimeters (about 2 inches) or less and hasn’t spread outside your adrenal gland.
* Stage II: The tumor is larger than 5 cm but hasn’t spread outside your adrenal gland.
* Stage III: The tumor has spread to nearby lymph nodes.
* Stage IV: The tumor has spread to nearby lymph nodes, nearby organs or more distant organs.

Cancer staging information can be confusing, so don’t hesitate to ask your healthcare provider to explain the system and how it applies to your situation.

**Management and Treatment**

The most common treatment is adrenalectomy to remove one or both of your adrenal glands. Often, healthcare providers prescribe additional medications like:

* Mitotane (Lysodren®): This drug limits adrenal gland activity, which may reduce the risk that adrenocortical carcinoma will come back. Providers use this medication after surgery to remove one adrenal gland or if surgery isn’t an option. Because this medication shuts down hormone production, people who receive it also take replacement medication.
* Metyrapone (Metopirone®): Providers may prescribe this and similar drugs to ease symptoms that happen when tumors produce excess hormones.

In some cases, however, the condition isn’t diagnosed until after tumors have grown too large to be safely removed with surgery. In those instances, healthcare providers may treat cancerous tumors with chemotherapy. This treatment won’t eliminate the cancerous tumors, but it can ease symptoms and slow down tumor growth.

You also may want to consider palliative care as part of your treatment. Palliative care is treatment that helps manage disease symptoms and treatment side effects. Palliative care specialists can also help you with emotional and mental health support.

**Complications or side effects of treatment**

Surgery and medications may cause different complications or side effects. For example, surgery to remove an adrenal gland may:

* Affect hormone production: Usually, your remaining adrenal gland takes over for the missing gland to make enough hormones (adrenal insufficiency). When that doesn’t happen, you may need to take replacement hormone tablets until your remaining gland starts to produce enough hormones.
* Cause infection: You may develop an infection in your abdomen or the surgical site.
* Cause excessive bleeding: This can happen during or after surgery.

**What are medication complications or side effects?**

Your healthcare provider may recommend that you take mitotane for two to five years after surgery. Mitotane side effects may include:

* Nausea and vomiting.
* Diarrhea.
* Rashes.
* Confusion.

**Outlook / Prognosis**

**What are survival rates for adrenocortical carcinoma?**

Overall, 50% of people with adrenocortical carcinoma were alive five years after diagnosis. Survival rates vary widely, depending on factors like:

* Tumor stage at diagnosis.
* Whether the tumor was functioning (producing hormones) or nonfunctioning.
* Your age.
* Your overall health.

Five-year survival rates by stage are:

| **Stage** | **Survival rate** |
| --- | --- |
| Stages I and II | 74% |
| Stage III | 54% |
| Stage IV | 38% |

Survival rate information may make you feel anxious or afraid. That’s understandable. Try to remember that these estimates are based on experiences that happened in the past. Experts measure survival rates every five years. Many things can change in five years that may make a difference. It’s also important to remember that survival rates aren’t estimates for how long you will live.

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. Researchers know about half of all cases of adrenocortical carcinoma happen when certain genes mutate and create cancerous cells that multiply and become tumors. But they don’t know what triggers those mutations, so they can’t recommend ways you could prevent them from happening.

But some inherited disorders increase your risk of developing this condition. If you have a family history of one of these disorders, talk to a healthcare provider about genetic tests that detect the mutations that cause these disorders.

**Living With**

Adrenocortical carcinoma is a rare cancer that often comes back — two challenges that may make you feel afraid, isolated or anxious. Fortunately, there are steps you can take that may help:

* Find support: Ask your healthcare team about support groups for people with adrenocortical carcinoma. It may help to spend time with or talk to people who know what you’re going through.
* Consider cancer survivorship programs: Many people with adrenocortical carcinoma feel anxious about cancer coming back. Cancer survivorship programs are one resource for dealing with that anxiety.
* Continue palliative care: You may need post-surgery chemotherapy and want help managing treatment side effects.

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

Adrenocortical carcinoma often comes back (recurs), most commonly within the first two years after surgery Your provider will set up a schedule of follow-up appointments to monitor for signs of recurrence. For example, you may have:

* Imaging tests: You may have tests every three months for two years, and then every three to six months for three more years.
* Blood tests: Your provider will do regular tests to check on hormone levels.

**Differential Diagnoses of Adrenocortical Carcinoma (ACC)**

* Adrenocortical adenoma (ACA) — benign adrenal cortical tumor, usually smaller and lipid-rich
* Adrenal metastases — secondary tumors from lung, kidney, melanoma, etc.
* Pheochromocytoma — catecholamine-producing adrenal medulla tumor
* Myelolipoma — benign tumor containing fat and hematopoietic tissue
* Adrenal cyst
* Ganglioneuroma
* Adrenal hematoma — often post-trauma or anticoagulation
* Soft tissue sarcomas of adrenal
* Primary adrenal lymphoma
* Neuroblastoma (especially in neonates)
* Congenital adrenal hyperplasia (in differential diagnosis of adrenal masses)
* Renal cell carcinoma invading adrenal
* Hepatocellular carcinoma metastasis to adrenal

Based on Morphology (Cytomorphological Features)

* Conventional ACC
* Oncocytic ACC — >90% oncocytic tumor cells
* Myxoid ACC — prominent extracellular mucin deposition
* Sarcomatoid ACC — resembles sarcomas, often with adrenal differentiation
* Carcinosarcoma
* Adenosquamous ACC
* Clear cell ACC

**EPIDEMIOLOGY**

Adrenal tumors are found in about 1 in every 10 people who have an imaging test (like a CT or MRI) of the adrenal gland. Most are benign adenomas.

Adrenocortical carcinomas are much less common than adenomas. In fact, they are very rare. The exact number diagnosed in the United States each year is not known. It is probably around 200 per year.

Patients with adrenocortical carcinoma are usually either very young (less than 5 years old) or middle-aged (40 to 50s). Women appear to be more likely to develop this cancer than men.

Adrenal cancer staging can be complex. If you have any questions about your stage, please ask your doctor to explain it to you in a way you understand.

| **ENSAT stage** | **AJCC Stage** | **Stage grouping** | **Stage description** |
| --- | --- | --- | --- |
| I | I | T1  N0  M0 | The tumor is 5 cm (about 2 inches) or less in size and it has not grown into tissues outside the adrenal gland (T1).  It has not spread to nearby lymph nodes (N0) or distant sites (M0). |
| II | II | T2  N0  M0 | The tumor is greater than 5 cm (2 inches) in size and it has not grown into tissues outside the adrenal gland (T2).  It has not spread to nearby lymph nodes (N0) or distant sites (M0). |
| III | III | T1  N1  M0 | The tumor is 5 cm (about 2 inches) or less in size and it has not grown into tissues outside the adrenal gland (T1).  The cancer has spread to nearby lymph nodes (N1) but not to distant sites (M0). |
| OR | |
| T2  N1  M0 | The tumor is greater than 5 cm (2 inches) in size and it has not grown into tissues outside the adrenal gland (T2).  The cancer has spread to nearby lymph nodes (N1) but not to distant sites (M0). |
| OR | |
| T3  Any N  M0 | The tumor is growing in the fat that surrounds the adrenal gland. The tumor can be any size (T3).  It might or might not have spread to nearby lymph nodes (Any N0).  It has not spread to distant sites (M0). |
| OR | |
| T4  Any N  M0 | The tumor is growing into nearby organs, such as the kidney, pancreas, spleen, and liver or large blood vessels (renal vein or vena cava). The tumor can be any size (T4).  It may or may not have spread to nearby lymph nodes (Any N).  It has not spread to distant organs (M0). |
| IV | IV | Any T  Any N  M1 | The cancer has spread to distant sites like the liver or lungs (M1). It can be any size (Any T) and may or may not have spread to nearby tissues (Any T) or lymph nodes (Any N). |

The following additional categories are not listed on 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

**What questions should I ask my healthcare provider?**

What does it mean if a tumor is functioning or non-functioning?

* A functioning tumor produces excess hormones such as cortisol, aldosterone, androgens, or estrogens, which can cause symptoms like Cushing’s syndrome, virilization, feminization, or high blood pressure.
* A non-functioning tumor does not produce excess hormones and may not cause hormonal symptoms, often presenting due to mass effect or incidental discovery.

Has the tumor spread outside my adrenal gland?

* ACC often invades nearby tissues or metastasizes to distant organs (liver, lungs, lymph nodes) by the time of diagnosis. Imaging studies like CT, MRI, or PET scans are used to determine if the tumor has spread.

If so, how far has it spread?

* The extent of spread is assessed by imaging and biopsy if needed. It may be limited to local invasion, regional lymph nodes, or distant metastases. This staging guides treatment and prognosis.

What are my treatment choices?

* The main treatment is surgical removal of the tumor (adrenalectomy).
* Additional treatments may include mitotane therapy (a drug targeting adrenal tissue), chemotherapy, radiation, or targeted therapies depending on stage and tumor behavior.
* For advanced or metastatic disease, systemic therapies and clinical trials may be options.

What are treatment side effects?

* Surgery may cause pain, bleeding, and hormonal imbalances requiring replacement therapy.
* Mitotane can cause gastrointestinal symptoms, neurological effects, and requires hormone monitoring.
* Chemotherapy and radiation have typical side effects like fatigue, nausea, and risk of infection.

Should my family members have genetic testing for the mutations that cause adrenocortical carcinoma?

* Most ACC cases are sporadic, but some are linked to inherited genetic syndromes (e.g., Li-Fraumeni syndrome, Lynch syndrome).
* If there is a family history of ACC or related cancers, or if you have a known genetic mutation, genetic counseling and testing for family members may be recommended.

Assuming treatment works, what are the chances the tumor will come back?

* ACC has a high risk of recurrence even after complete surgical removal, especially in advanced stages.
* The overall 5-year survival rate is about 50%, but recurrence rates are significant, so close follow-up is essential.

| **Genetic disease**  **Gene and chromosomal involvement** | **Organ involvement** |
| --- | --- |
| Beckwith-Wiedemann syndrome  CDKN1C mutation  KCNQ10T1, H19 (epigenetic defects) 11p15 locus alterations  IGF-2 overexpression | Macrosomia, macroglossia, hemihypertrophy (70%), omphalocele, Wilm’s tumor, ACC (15-  20% adrenocortical tumors) |
| Li-Fraumeni syndrome P53(17p13) | Soft tissue sarcoma, breast cancer, brain  tumors, leukemia, ACC |
| Multiple Endocrine Neoplasia syndrome 1  Menin (11q13) | Parathyroid, pituitary, pancreatic, bronchial tumors  Adrenal cortex tumors (30%, rarely ACC) |
| Familial Adenomatous polyposis  APC (5q12-22) | Multiple adenomatous polyps and cancer colon and rectum  Periampullary cancer, thyroid tumors,  hepatoblastoma, rarely ACC |
| SBLA syndrome | Sarcoma, breast and lung cancer, ACC |
| Neurofibromatosis  NF1 | Six or more light brown dermatological spots ("café au lait spots  At least two neurofibromas |
| Carney Complex  PRKAR1A not defined | Lentigines, Atrial Myxoma, and Blue Nevi |

Immunotherapy in Patients with ACC

| **Molecule** | **Phase** | **Population(n)** | **Prior systemic treatment** | **Results** |
| --- | --- | --- | --- | --- |
| Pembrolizomab 200 mg every 3  w (35 cycles) | IΙ | 39 | 28 | PFS=2.1,OS=24.9 ORR (RECIST)=23% |
| Pembrolizomab 200 mg every 3  w (35 cycles) | II | 16 | 16 | SD at 27 w=36%, ORR(RECIST)=14% |
| Nivolumab 240 mg every 2 w | II | 10 | 10 | PFS=1.8, ORR=11% |
| Avelumab 10 mg/kg every 2 w (±mitotane) | Ib | 50 | 50 | PFS=2.6, OS=10.6, ORR=6% |
| Ipilimumab 1 mg/kg intravenously every 6 weeks with nivolumab 240 mg intravenously every 2 weeks | II | 21 | 21 | 6-month OS = 76%; the median OS= 15.8 months, ORR=14% |
| Camrelizumab combined with apatinib | II | 21 | 21 | ORR=52%, median PFS=3.3 months, median OS=20.9 months |

**doctor-patient conversation about adrenocortical carcinoma (ACC)**,

Doctor: Hello, thank you for coming in today. I want to discuss your diagnosis of adrenocortical carcinoma and what you can expect moving forward.

Patient: Thank you, doctor. What exactly is adrenocortical carcinoma?

Doctor: It is a rare cancer that starts in the outer layer of your adrenal gland, which produces important hormones. Because it’s rare, we will take a careful, multidisciplinary approach to your care.

Patient: Has the tumor spread outside my adrenal gland?

Doctor: We’ve done imaging tests, and currently, the tumor appears confined to your adrenal gland, which is good news. However, ACC can spread to nearby lymph nodes or distant organs, so we’ll monitor closely.

Patient: What are my treatment choices?

Doctor: The main treatment is surgery to remove the affected adrenal gland, called an adrenalectomy. Depending on the tumor size and spread, we may also recommend additional treatments like mitotane, chemotherapy, or radiation. Clinical trials may be an option too.

Patient: What side effects should I expect from treatment?

Doctor: Surgery recovery can take several weeks, and you may need hormone replacement if the other adrenal gland isn’t functioning well. Medications like mitotane can cause nausea, fatigue, and require close monitoring. Chemotherapy and radiation have their own side effects, but we will manage these carefully.

Patient: Should my family members have genetic testing?

Doctor: ACC can sometimes be linked to inherited genetic mutations, especially TP53 mutations seen in syndromes like Li-Fraumeni. If you have a family history of related cancers, genetic counseling and testing for your family may be recommended.

Patient: If treatment works, what are the chances the tumor will come back?

Doctor: ACC has a relatively high risk of recurrence, even after successful treatment. That’s why regular follow-up with imaging and lab tests is essential. We will work together to catch any recurrence early.

Patient: What support will I have during this process?

Doctor: You will be cared for by a multidisciplinary team including endocrinologists, surgeons, oncologists, genetic counselors, and supportive care specialists. We’ll provide resources and support every step of the way.

REFERENCES

https://www.ncbi.nlm.nih.gov/books/NBK278924/ https://emedicine.medscape.com/article/276264-differential

[Adrenocortical Carcinoma: Symptoms, Stages & Prognosis](https://my.clevelandclinic.org/health/diseases/6152-adrenocortical-carcinoma#overview)

**Follicular thyroid cancer**

Follicular thyroid cancer is a type of thyroid cancer. Your thyroid is a gland in your neck and is part of your endocrine system. It makes hormones that help control your metabolism and blood calcium levels. When cells in your thyroid grow in ways they shouldn’t, thyroid cancers can develop.

**Types of thyroid cancer**

There are four types of thyroid cancer:

* Follicular.
* Papillary.
* Medullary.
* Anaplastic.

Pathologists examine the cancer cells under a microscope to diagnose which type of thyroid cancer it is. Thyroid cancers may be:

* Well-differentiated: These thyroid tumors are treatable and often curable. Follicular thyroid cancer and papillary thyroid cancer are well-differentiated cancers.
* Undifferentiated: These tumors are harder to treat. Anaplastic thyroid cancer is a rare, undifferentiated cancer and is the most aggressive type of thyroid cancer.

**Follicular thyroid cancer and papillary thyroid cancer**

These two types of thyroid cancers are fairly similar. They both start in the follicular cells of your thyroid gland. Papillary thyroid cancer is more likely to spread to your lymph nodes than follicular thyroid cancer. Papillary thyroid cancer is also more common than follicular thyroid cancer.

**Follicular thyroid cancer and medullary thyroid cancer**

Medullary thyroid cancers are neuroendocrine tumors. This cancer occurs in the C-cells of your thyroid and often runs in families. C-cells make calcitonin, which regulates calcium levels in your blood. Medullary thyroid cancers are more aggressive and less differentiated than follicular thyroid cancers. They are more likely to spread to lymph nodes and other areas of your body.

**Who does follicular thyroid cancer affect?**

Anyone can get follicular thyroid cancer, but it occurs more often in older women.

**How common is follicular thyroid cancer?**

Between 10% and 15% of all thyroid cancers are follicular thyroid cancer. Most people with thyroid cancer have papillary thyroid cancer (between 70% and 80% of all thyroid cancers).

**How will follicular thyroid cancer affect me?**

Follicular thyroid cancer can sometimes cause a lump or pain in your neck. If your healthcare provider diagnoses cancer early, treatment may cure you. Without treatment, follicular cancer can spread (metastasize) to other parts of your body. Metastasized cancer is harder to treat.

**Symptoms and Causes**

You might not have any symptoms of follicular thyroid cancer. But you might have:

* A lump (thyroid nodule) in your neck.
* Ear pain, or pain in your jaw or neck.
* Hoarseness (dysphonia).
* Swollen lymph nodes in your neck.
* Trouble breathing or swallowing (dysphagia).

**What causes follicular thyroid cancer?**

Follicular cancer happens when cells in the thyroid gland grow in ways they shouldn’t. Healthcare providers don’t always know why these cancers occur. Thyroid cancer is more common in people who were exposed to radiation, like if you had radiation therapy or work near radiation.

**Is follicular thyroid cancer contagious?**

Follicular thyroid cancer is not contagious.

**How long does it take for follicular thyroid cancer to spread?**

There’s no way to know if follicular thyroid cancer will spread or how long it will take. Metastasis can happen right away or after a few years.

**Diagnosis and Tests**

Your healthcare provider may notice a lump in your neck during a physical examination. Providers may also find a nodule during imaging tests for other conditions. Your provider might find or confirm a nodule during:

* CT scan.
* MRI.
* Ultrasound.
* X-ray.

Many thyroid nodules are noncancerous (benign). If your healthcare provider thinks a nodule may be cancer, they may recommend a fine needle biopsy. Experts in cytology examine fluid from the nodule under a microscope to look for cancer cells.

**Management and Treatment**

Providers treat most follicular thyroid cancers with surgery. They may remove:

* Part of the gland where the tumor is (lobectomy).
* The entire gland (total thyroidectomy).
* Nearby lymph nodes, if cancer has spread to your lymph nodes.

**What other treatments do healthcare providers use for follicular thyroid cancer?**

Depending on what stage cancer is in and if it has spread to other organs, your provider may recommend additional treatment after surgery. This can include:

* Chemotherapy.
* Radiation therapy.
* Radioiodine (radioactive iodine) therapy.
* Targeted therapy (drugs that destroy specific cancer cells).
* Thyroid hormone therapy.

**Side effects of follicular thyroid cancer treatment**

Cancer treatments can cause different side effects. You might have:

* Diarrhea.
* Loss of appetite.
* Fatigue.
* Hair loss.
* Nausea and vomiting.
* Speech and swallowing problems.
* Trouble concentrating or remembering things (chemo brain).
* Weakness.

**How long will I need treatment for follicular thyroid cancer?**

Your healthcare provider will check your response to treatment. When cancer is no longer present, you won’t need active treatment anymore. If healthcare providers remove your thyroid gland, you may need to take thyroid hormone replacement medication to stay healthy.

**Outlook / Prognosis**

Talk with your healthcare provider about what stage cancer is in and the recommended treatment plan. Your provider can help you manage treatment side effects so you can continue to work and participate in daily activities.

**Is follicular thyroid cancer curable?**

Follicular thyroid cancer is often curable, especially if diagnosed early. Talk to your healthcare provider right away if you:

* Notice any thyroid cancer symptoms.
* Have risk factors for thyroid cancer.

**Prevention**

You can’t do much to reduce your risk of developing follicular thyroid cancer. Talk to your healthcare provider if you have a family history of cancer or other risk factors. They can discuss any preventive steps you need to take.

**Living With**

**How do I take care of myself if I have follicular thyroid cancer?**

See your healthcare provider for follow-up care after you finish treatment. Your provider may recommend certain blood tests to monitor thyroid hormone levels to make sure cancer isn’t coming back (recurring).

**Epidemiology**

Frequency

United States

The American Cancer Society (ACS) estimates that in 2024, 44,020 new thyroid cancers will occur, 31,520 in women and 12,500 in men; the ACS estimates that 2170 deaths from thyroid cancer will occur, 1180 in women and 990 in men. In women, thyroid cancer is the eighth most common cancer, accounting for approximately 3% of all new cases.In the United States, about 10-15% of all thyroid cancers are follicular.

International

Thyroid cancers account for 1.5% of all cancers in adults and 3% in children. The European Network of Cancer Registries reports that the incidence varies from country to country: Lithuania reported the highest age-standardized rate per 100,000 population (15.5), followed by Italy (13.5), Austria (12.4), Croatia (11.4), and Luxembourg (11.1). The highest incidence of thyroid carcinomas in the world is among female Chinese residents of Hawaii. In Hawaii, the incidence of FTC ranges from 10-3 new cases a year per million inhabitants.

In recent years, the frequency of FTC has appeared to increase; however, this increase is related to improvement in diagnostic techniques and a successful campaign of information about this carcinoma.

Of all thyroid cancers, 17-20% are follicular. According to world epidemiologic data, follicular carcinoma is the second most common thyroid neoplasm; in some geographic areas, however, FTC is the most common thyroid tumor. The relative incidence of follicular carcinoma is higher in areas of endemic goiter.

Race-, sex-, and age-related demographics

FTC occurs more frequently in Whites than in Blacks. The incidence is higher in women than men by a factor of 2-3 or more. The female-to-male ratio varies by patient age: it is 4:1 in patients younger than 19 years and older than 45 years, and 3:1 in patients 20-45 years.

In postmenopausal women, a weak positive association (relative risk < 1.20) has been found between increased body mass index and thyroid cancer.

Thyroid carcinoma occurs in all age groups, but is most oftten diagnosed in persons aged 45–64 years. Median age at diagnosis is 51 years.In older adults, FTC tends to occur more often than papillary thyroid carcinoma.

**Differential Diagnoses**

* Anaplastic Thyroid Carcinoma
* Goiter
* Graves' Disease
* Hurthle Cell Carcinoma (Oncocytic Carcinoma)
* Medullary Thyroid Carcinoma
* Papillary Thyroid Carcinoma
* Thyroid Nodule
* Toxic Nodular Goiter

**Staging**

The accurate assessment of the proliferative grade and the extent of invasion have high prognostic value and are mandatory in every specimen.

The staging of well-differentiated thyroid cancers is related to age for the first and second stages but not for the third and fourth stages.

In patients younger than 45 years, staging is as follows:

* Stage I: Any T, any N, M0 (Cancer is in the thyroid only.)
* Stage II: Any T, any N, M1 (Cancer has spread to distant organs.)

In patients older than 45 years, staging is as follows:

* Stage I: T1, N0, M0 (Cancer is in the thyroid only, in one or both lobes.)
* Stage II: T2, N0, M0 and T3, N0, M0 (Cancer is in the thyroid only and is larger than 1.5 cm.)
* Stage III: T4, N0, M0 and any T, N1, M0 (Cancer has spread outside the thyroid but not outside of the neck.)
* Stage IV: Any T, any N, M1 (Cancer has spread to other parts of the body.)

The guidelines provide initial risk estimates and re-stratification based on response to initial therapy.

For initial risk estimates, patients are considered at low risk if all of the following are present:

* No local or distant metastases
* All macroscopic tumor has been resected
* No invasion of locoregional tissues
* Tumor does not have aggressive histology (eg, tall cell, insular, columnar cell carcinoma, Hürthle cell carcinoma, FTC)
* No vascular invasion
* No iodine-131 (131I) uptake outside the thyroid bed on the post-treatment scan, if done

Patients are considered at intermediate risk if any of the following is present:

* Microscopic invasion into the perithyroidal soft tissues
* Cervical lymph node metastases or 131I uptake outside the thyroid bed on the post-treatment scan done after thyroid remnant ablation
* Tumor with aggressive histology or vascular invasion (eg, tall cell, insular, columnar cell carcinoma, Hürthle cell carcinoma, FTC)

Patients are considered at high risk if any of the following is present:

* Macroscopic tumor invasion
* Incomplete tumor resection with gross residual disease
* Distant metastases

The ATA guidelines define response to initial therapy (6–24 months after radioactive iodine ablation) as excellent if all the following are present:

* Suppressed and stimulated thyroglobulin (Tg) < 1 ng/mL
* No evidence of disease on neck ultrasound (US)
* Negative cross-sectional and/or nuclear medicine imaging (if performed)

Response is defined as acceptable if any of the following are present:

* Suppressed Tg < 1 ng/mL and stimulated Tg ≥ 1 and < 10 ng/mL
* Neck US with nonspecific changes or stable sub-centimeter lymph nodes
* Cross-sectional and/or nuclear medicine imaging with nonspecific changes, although not completely normal

Response is defined as incomplete if any of the following are present:

* Suppressed Tg ≥ 1 ng/mL or stimulated Tg ≥ 10 ng/mL
* Rising Tg values
* Persistent or newly identified disease on cross-sectional and/or nuclear medicine imaging

A comparison study in 98 patients with FTC concluded that the ATA staging system predicts recurrence rate and survival better than TNM staging. Hazard ratios were 4.67 with ATA staging versus 1.26 for TNM staging

**QUESTION AND ANSWER SET**

What is follicular thyroid cancer?

Follicular thyroid cancer is the second most common type of thyroid cancer, accounting for about 10–15% of all thyroid cancers. It arises from the follicular cells of the thyroid gland and typically affects adults aged 40 to 60 years. It is more common in women than men by about a 3:1 ratio.

2. What are the common symptoms of follicular thyroid cancer?

Most patients notice a lump or nodule in the neck. Symptoms like difficulty swallowing or breathing are less common unless the tumor grows large. Many nodules are found incidentally during imaging for other reasons.

3. How does follicular thyroid cancer spread?

FTC rarely spreads to lymph nodes (about 12% of cases), unlike papillary thyroid cancer. It more commonly invades blood vessels within the thyroid and can spread hematogenously to distant sites such as the lungs and bones.

4. How is follicular thyroid cancer diagnosed?

Diagnosis involves physical exam, ultrasound, and fine needle aspiration (FNA) biopsy. However, FNA cannot reliably distinguish follicular adenoma from carcinoma because it cannot assess capsular or vascular invasion. Definitive diagnosis requires surgical removal and histopathology.

5. What are the treatment options?

The primary treatment is surgery, typically a thyroid lobectomy or total thyroidectomy depending on tumor size and extent. After surgery, radioactive iodine therapy may be recommended to ablate residual tissue and treat metastases. Lifelong thyroid hormone replacement therapy is needed if the entire gland is removed.

6. What is the prognosis for follicular thyroid cancer?

The overall prognosis is excellent, especially for small tumors (<1 cm) and younger patients, with cure rates near 95%. Prognosis worsens with larger tumors, vascular invasion, distant metastases, or older age.

7. Is follicular thyroid cancer hereditary?

Most follicular thyroid cancers are not hereditary. Familial cases are rare, and routine genetic testing is not recommended unless there is a strong family history or syndromic features.

8. How often should I have follow-up after treatment?

Follow-up includes periodic physical exams, ultrasound, and blood tests (thyroglobulin levels) to monitor for recurrence. The frequency depends on initial tumor stage and risk factors.

9. What side effects can I expect from treatment?

Surgery risks include damage to the recurrent laryngeal nerve (affecting voice) and hypoparathyroidism (low calcium). Radioactive iodine can cause dry mouth, altered taste, and rare long-term effects. Thyroid hormone therapy side effects depend on dosing.

10. Can follicular thyroid cancer be prevented?

There are no specific prevention strategies. Adequate iodine intake may reduce risk in some populations. Early detection and treatment are key to good outcomes

**Genetic Alterations in Follicular Thyroid Cancer**

* RAS gene mutations (HRAS, KRAS, NRAS) are the most frequent mutations in FTC, occurring in approximately 17% to 57% of cases. These mutations activate the MAPK and PI3K/AKT signaling pathways, promoting tumor growth. NRAS mutations are the most common among the RAS family in FTC.
* PAX8-PPARγ gene fusion is found in about 12% to 53% of FTC cases. This fusion protein acts as an oncogene by inhibiting the tumor suppressor activity of PPARγ, though it does not clearly affect prognosis.
* TERT promoter mutations occur in around 15% of FTCs and are associated with more aggressive clinical features and poorer prognosis.
* TSH receptor mutations are found in about 10% of FTC cases and appear to be mutually exclusive with RAS mutations.
* Other less common mutations include PIK3CA, AKT1, PTEN (involved in the PI3K/AKT pathway), and mutations in genes such as EIF1AX, DICER1, EZH1, which have been identified by next-generation sequencing studies.
* FTC tumors generally have a lower mutational burden compared to other cancers and are considered genetically simpler.
* Follicular variant papillary thyroid carcinomas (FVPTC) share some molecular features with FTC, including enrichment of RAS mutations and PAX8-PPARγ fusions, reflecting their follicular architecture.
* BRAF mutations, common in papillary thyroid carcinoma (PTC), are rare in FTC.

**DOCTOR PATIENT CONVERSATION**

Doctor: Hello, I want to discuss the results of your thyroid biopsy and what they mean. You have a type of thyroid cancer called follicular thyroid cancer.

Patient: What exactly is follicular thyroid cancer?

Doctor: It’s a cancer that starts in the follicular cells of your thyroid gland, which produce thyroid hormones. It’s the second most common type of thyroid cancer and usually grows slowly.

Patient: How serious is it? Has it spread?

Doctor: Follicular thyroid cancer tends to spread through the bloodstream rather than lymph nodes, often to the lungs or bones if it spreads. We’ll do imaging tests to check if it has spread beyond your thyroid.

Patient: How do you treat it?

Doctor: The main treatment is surgery to remove part or all of your thyroid gland. Sometimes, after surgery, we use radioactive iodine to destroy any remaining thyroid tissue or cancer cells. You may also need thyroid hormone replacement afterward.

Patient: What are the side effects of treatment?

Doctor: Surgery risks include changes to your voice or calcium levels, but these are usually temporary. Radioactive iodine can cause dry mouth or altered taste. We’ll monitor you closely and manage any side effects.

Patient: What is my prognosis?

Doctor: The prognosis is generally excellent, especially if the cancer is caught early and treated properly. Most patients do very well.

Patient: Will I need follow-up?

Doctor: Yes, regular follow-up with blood tests and ultrasounds is important to detect any recurrence early.

Patient: Should I be worried about my family?

Doctor: Follicular thyroid cancer is usually not hereditary, so routine genetic testing for family members isn’t typically needed unless there’s a strong family history.

Patient: Thank you, doctor. This helps me understand what to expect.

Doctor: You’re welcome. Please write down any questions you have for our next visit, and feel free to bring a family member for support.

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**Medullary thyroid cancer**

Medullary thyroid cancer (MTC) is cancer that forms inside your thyroid gland. The inside is called the medulla. It contains special cells called parafollicular C cells that make calcitonin, a hormone. MTC happens when the C cells grow out of control.

Hearing you might have cancer can leave you with many questions and worries, especially when it’s rare. Know that your healthcare team will be by your side along the way. Several therapies can help treat MTC.

Thyroid cancer, in general, is fairly common. But medullary thyroid cancer, specifically, is rare. Approximately 4% to 10% of all thyroid cancers in the United States are MTC. About 1,000 people receive an MTC diagnosis each year in the U.S.

**Symptoms and Causes**

Symptoms of medullary thyroid cancer include:

* A nodule (lump) on the upper part of your thyroid gland (75% to 95% of people have this at diagnosis)
* Swollen lymph nodes in your neck (70% of people have this at diagnosis)

In rare cases, an enlarged thyroid nodule can cause:

* Hoarseness
* Difficulty swallowing
* Breathing issues

In some cases, people have MTC for a long time before they notice symptoms. This is because the tumor remains small.

**What causes medullary thyroid cancer?**

About 75% of medullary thyroid cancer (MTC) cases (3 in 4) are sporadic. This means it happens in people who don’t have a family history of MTC. Scientists haven’t yet figured out the exact cause of sporadic MTC. But 40% to 50% of people with sporadic MTC have acquired mutations in the *RET* gene. This means you develop the genetic mutation later in life — you aren’t born with it.

In up to 25% of cases (1 in 4), MTC is due to an inherited condition called multiple endocrine neoplasia type 2 (MEN2). There are different subtypes of MEN2, including:

* MEN2A. People with MEN2A have a high chance (90%) of getting MTC.
* MEN2B. Some cases of MEN2B are inherited. But most of the time, it isn’t. People with MEN2B have an 100% chance of getting MTC at a very young age.

There’s also a subvariant of MEN2B called familial medullary thyroid cancer (FMTC). People with FMTC have a *RET* gene mutation but only develop MTC (not other tumors).

If you have the *RET* gene mutation, you may be able to get preventive surgery to remove your thyroid gland before cancer develops.

**Diagnosis and Tests**

Medullary 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 exam. Sometimes, providers discover it accidentally with imaging tests you get for other reasons.

Your provider will likely recommend the following tests to help diagnose MTC:

* Imaging tests. Imaging tests can help identify the nodule on your thyroid. These tests might include thyroid ultrasound, a CT scan and/or MRI.
* Fine needle aspiration (needle biopsy). Your provider will likely want to take a small tissue sample (biopsy) from the nodule on your thyroid. They’ll use a very thin needle.
* Blood tests. These may include tests that measure your levels of calcitonin and carcinoembryonic antigen (CEA). These levels are typically elevated in people with MTC.

Your provider may also recommend genetic testing to see if you have MEN2. If you do, they’ll recommend genetic testing for your biological family members, as well.

**Management and Treatment**

The main treatment for MTC is surgery to remove your entire thyroid gland (total thyroidectomy).

If the thyroid cancer has spread (metastasized) to lymph nodes in your neck, your surgeon will likely remove them, as well. After surgery, you’ll need to take thyroid hormone replacement medications for the rest of your life.

Other than surgery, your healthcare provider may recommend other treatments, including:

* Radiation therapy
* Chemotherapy
* Targeted therapies that act on changes in DNA found in some cases of MTC (vandetanib and cabozantinib)

After treatment for MTC, your provider will check your levels of CEA and calcitonin through blood tests. This way, they can keep track of how well the treatment is working or if the cancer has come back.

MTC is usually more aggressive than the other, more common types of thyroid cancer. It’s easier to treat and manage if it’s found before it spreads to lymph nodes in your neck or other parts of your body.

**Outlook / Prognosis**

The prognosis (outlook) for medullary thyroid cancer (MTC) depends on several factors, including:

* The stage of the cancer
* If the cancer has spread to other parts of your body (metastasized)
* How much of the tumor was taken out during surgery
* Your age and overall health

The prognosis of MTC is usually not as good as papillary and follicular thyroid cancers. But if you and your provider discover MTC early, surgery can cure it. Even if the diagnosis is delayed, MTC often progresses (gets worse) relatively slowly.

A worse prognosis may affect those:

* Who are over 65 years
* Have late-stage cancer
* Have incomplete surgical removal of the tumor

**What is the life expectancy of medullary thyroid cancer?**

Current research estimates that the five-year survival rate for stages 1 to 3 of medullary thyroid cancer is 93%. It’s 28% for stage 4.

It’s important to note that since there are so few new MTC cases diagnosed each year, these survival rates may not be very accurate. Your healthcare team will give you a better idea of what to expect.

**What’s the difference between papillary and medullary thyroid cancer?**

Papillary thyroid cancer is the most common type of thyroid cancer. It represents about 80% of all thyroid cancer diagnoses. Medullary thyroid cancer (MTC) is rare.

Papillary thyroid cancer begins in the thyroglobulin-producing follicular cells in your thyroid. MTC arises from calcitonin-producing cells in your thyroid. Thyroglobulin is a protein, and calcitonin is a hormone.

Papillary thyroid cancer is often linked to radiation exposure, whereas MTC isn’t.

**EPIDEMIOLOGY**

MTC accounts for approximately 1% to 5% of all thyroid cancers in the United States and globally.Sporadic MTC typically peaks in incidence during the fifth or sixth decade of life. In contrast, MTC associated with MEN2A or 2B can present as early as childhood or the first decade of life, while patients with FMTC usually present in the second or third decade. The age of presentation is closely linked to specific *RET* gene mutations. Unlike other types of thyroid cancer, MTC does not exhibit a female predominance

**DIFFERENTIAL DIAGNOSIS**

Patients with medullary thyroid cancer have a clinical presentation similar to other thyroid diseases. The following differential diagnoses must be kept in mind while evaluating these patients.

* Papillary thyroid cancer
* Follicular thyroid carcinoma
* Oncocytic (Hürthle) thyroid carcinoma
* Anaplastic thyroid carcinoma
* Intestinal carcinoid tumor
* Thyroid lymphoma
* Thyrotoxicosis
* Toxic nodular goiter
* Graves' disease

**STAGING**

* **Stage I**: T1, N0, and M0
* **Stage II**: T2, N0, and M0 or T3, N0, and M0
* **Stage III**: T1 to T3, N1a, and M0
* **Stage IVA**: T4a, any N, and M0 or T1 to T3, N1b, and M0
* **Stage IVB**: T4b, any N M0
* **Stage IVC**: Any T, any N, and M1

**COMMON QUESTION AND ANSWER SET**

What is medullary thyroid cancer?

Medullary thyroid cancer is a rare type of thyroid cancer that arises from the parafollicular or C cells of the thyroid gland, which produce the hormone calcitonin. It accounts for about 2–4% of all thyroid cancers.

2. What causes medullary thyroid cancer?

MTC can occur sporadically or be inherited. About 25–35% of cases are hereditary, caused by mutations in the RET proto-oncogene. Genetic testing and counseling are important for patients and their families.

3. How is medullary thyroid cancer diagnosed?

Diagnosis involves measuring serum calcitonin and carcinoembryonic antigen (CEA) levels, which are typically elevated. Imaging tests such as neck ultrasound, CT scans, and sometimes PET scans help assess tumor extent and metastasis. A biopsy confirms the diagnosis.

4. What are the stages of medullary thyroid cancer?

* Stage I: Tumor ≤2 cm confined to thyroid
* Stage II: Tumor >2 cm or spread to nearby muscles
* Stage III: Spread to lymph nodes near the trachea or larynx
* Stage IV: Spread to soft tissues, distant lymph nodes, or distant organs like lungs or liver.

5. What are the treatment options?

Surgery is the primary treatment, usually a total thyroidectomy with central lymph node dissection. Additional treatments may include external beam radiation, targeted therapies, and rarely chemotherapy. Lifelong thyroid hormone replacement is necessary after surgery.

6. What are the side effects of treatment?

Surgery risks include voice changes, hypocalcemia due to parathyroid damage, and the need for lifelong hormone replacement. Radiation and targeted therapies have their own side effect profiles, which are managed by the care team.

7. How is follow-up managed?

Patients require lifelong monitoring with physical exams, serum calcitonin and CEA levels, and imaging to detect recurrence or metastasis. Follow-up is typically every 6 months for the first 2 years, then annually.

8. Can medullary thyroid cancer come back?

Yes, MTC can recur locally or metastasize to distant organs such as bones, liver, and lungs. Early detection through monitoring improves management.

9. Should family members be tested?

If a hereditary mutation is found, family members should undergo genetic counseling and testing to assess their risk and consider preventive measures.

10. Are there clinical trials available?

Because MTC is rare, clinical trials are important for developing new treatments. Patients should discuss trial options with their specialists

**Genomic Features of Medullary Thyroid Cancer**

* RET proto-oncogene mutations are the primary drivers of MTC.
* These mutations occur in about 50% of sporadic MTC cases and nearly all hereditary cases (familial MTC and MEN2 syndromes).
* The most common mutation in sporadic MTC is RET M918T, which is also characteristic of MEN2B and is associated with aggressive disease and poor prognosis.
* Other frequent RET mutations include codons 634, 609, 611, 618, and 620, especially in hereditary forms (MEN2A).
* Different RET mutations predict distinct clinical behaviors and guide treatment strategies.
* RAS gene mutations (HRAS, KRAS, NRAS) are found in approximately 70% of sporadic MTC cases that are RET wild-type.
* RAS mutations are mutually exclusive with RET mutations and define a separate molecular subgroup.
* BRAF mutations are rare but have been reported in some RET-negative MTC cases, suggesting alternative oncogenic drivers.
* Additional mutated genes identified in recent sequencing studies include SF3B1, KMT2A, CDKN1B, and others, though these are less common and their clinical significance is still being explored.
* Epigenetic alterations and miRNA expression differences have been observed between sporadic and hereditary MTC, indicating complex regulation beyond DNA mutations.

**doctor-patient conversation about medullary thyroid cancer (MTC)**,

Doctor: Hello, thank you for coming in today. I want to discuss the results of your tests. The biopsy and blood work show that you have medullary thyroid cancer, a rare type of thyroid cancer that arises from the hormone-producing C cells in your thyroid.

Patient: Medullary thyroid cancer? What does that mean exactly?

Doctor: It means the cancer started in a specific type of cell in your thyroid that makes a hormone called calcitonin. This type of cancer behaves differently from the more common thyroid cancers. We often measure calcitonin and another marker called CEA in your blood to help us monitor the disease.

Patient: Has the cancer spread anywhere else?

Doctor: We’ve done imaging tests like CT scans and ultrasounds. So far, it looks like the tumor is confined to your thyroid and possibly nearby lymph nodes, but we will keep monitoring carefully. Sometimes, MTC can spread to lymph nodes, lungs, or liver.

Patient: What are my treatment options?

Doctor: The main treatment is surgery to remove your entire thyroid gland and nearby lymph nodes to try to remove all the cancer. After surgery, we’ll monitor your calcitonin and CEA levels to check for any remaining cancer. In some cases, additional treatments like targeted therapies or radiation may be needed.

Patient: What are the risks or side effects of surgery?

Doctor: Surgery risks include changes in your voice because of nerve irritation, and possible low calcium levels if the parathyroid glands are affected. We monitor and manage these closely. You will also need lifelong thyroid hormone replacement after surgery.

Patient: Is this cancer hereditary? Should my family be tested?

Doctor: Medullary thyroid cancer can be hereditary in about 25–35% of cases, caused by mutations in the RET gene. We recommend genetic testing for you, and if a mutation is found, your family members should be offered genetic counseling and testing as well.

Patient: What is my prognosis?

Doctor: Many patients do well, especially if the cancer is caught early and completely removed. We will follow you closely with blood tests and imaging to catch any recurrence early.

Patient: What kind of follow-up will I need?

Doctor: Regular follow-up every 6 months to a year with blood tests for calcitonin and CEA, plus imaging as needed. Lifelong monitoring is important because MTC can recur years later.

Patient: This is a lot to take in, but I appreciate you explaining everything.

Doctor: I understand this is overwhelming. Please write down any questions you have, and bring a family member or friend to your next appointment. We are here to support you every step of the way.

REFERENCES

https://www.thyroidcancer.com/thyroid-cancer/medullary/genetics https://www.ncbi.nlm.nih.gov/books/NBK459354/#article-24906.s4 [Medullary Thyroid Cancer: What It Is, Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/22873-medullary-thyroid-cancer-mtc#overview)

**Seminoma cancer**

Seminoma is a type of germ cell tumor that most commonly affects one or both of your testicles (testicular cancer). In males, germ cells form sperm.

Although rare, seminoma is very curable and has a high survival rate with proper treatment. Treatment typically requires surgically removing your affected testicle. This won’t affect your ability to get an erection or orgasm or have biological children. If a provider must remove both testicles, you’ll still retain sexual function and, if you wish to have biological children, you can bank your sperm and use an assisted reproductive technique, like in vitro fertilization (IVF).

**Is a seminoma a cancer?**

Yes, testicular seminoma is a type of cancer. It usually affects your testicles. But it can also affect other areas of your body, including:

* The space in your chest (mediastinum) that contains your heart.
* The space behind your abdominal cavity (retroperitoneum), which includes your urinary system and kidneys.

**Types of seminoma**

There are two main subtypes of seminoma. These are:

* Classic (typical) seminoma.
* Spermatocytic seminoma.

Classic (typical) seminoma

Classic seminoma usually affects people between the ages of 25 and 45. It doesn’t cause your body to make higher levels of alpha-fetoprotein (AFP). AFP is a protein that develops in the liver during fetal development. High AFP levels in adults may be a sign of some types of cancer, including other subtypes of testicular cancer. But if you have classic seminoma, you don’t have elevated AFP.

Spermatocytic seminoma

Spermatocytic seminoma usually affects people ages 50 and older. It usually grows slowly and isn’t likely to spread to other areas of your body.

Testicular cancer is rare — it affects about 1 in 250 males. But the number of cases is increasing, which is attributed to an increase in seminoma. According to the U.S. Centers for Disease Control and Prevention (CDC), 54% of all testicular cancers diagnosed in the U.S. from 2001 to 2020 are seminomas. The American Cancer Society estimates there will be about 9,760 diagnosed cases of testicular cancer in the U.S. in 2024.

Even though testicular cancer overall is rare, it’s the most common cancer in males between 15 and 35 years old. According to the CDC, seminoma most commonly affects people in their 30s to 60s.

| **Age Group** | **Percentage of Seminoma Testicular Cancer Cases** |
| --- | --- |
| Younger than 15 | 3.9% |
| 15 to 29 | 32.1% |
| 30 to 44 | 63.6% |
| 45 to 64 | 73.2% |
| 65 or older | 57% |

**Symptoms and Causes**

Seminoma symptoms usually include swelling or a painless lump on your testicle. Other symptoms may include:

* A feeling of heaviness in your testicles, perineum or scrotum.
* A dull ache in your testicles, perineum or scrotum.

Rarely, you may also experience:

* Sudden, sharp (acute) pain in or around your testicles.
* Blood in your semen (hematospermia).

If seminoma spreads (metastasizes), symptoms may include:

* Lumps on the lymph nodes in your neck.
* Cough.
* Shortness of breath (dyspnea).
* Nausea and vomiting.
* Gastrointestinal bleeding.
* Bone pain.

**Is seminoma aggressive?**

In early stages, seminoma isn’t aggressive. But sometimes, it may grow quickly. If you have seminoma, a healthcare provider will monitor you to make sure it doesn’t spread.

**What causes seminoma?**

During typical fetal development, germ cells develop and eventually make their way to the fetus’s ovaries (ova or egg cells) or testicles (sperm). But if you have seminoma, your germ cells don’t develop into fully formed sperm. They divide and multiply, eventually growing into masses (tumors). Medical experts aren’t sure why germ cells sometimes don’t develop into typical sperm.

**Who does seminoma affect?**

Seminoma can affect anyone with testicles at any age. But you’re more likely to have seminoma if you:

* Are between your 30s and 60s.
* Are white.
* Have a personal or biological family history of seminoma.
* Have a personal history of undescended testicles.

**Diagnosis and Tests**

A healthcare provider can diagnose seminoma. They’ll:

* Review your medical history.
* Ask about your symptoms.
* Perform a physical exam, which will include checking your testicles or lymph nodes for lumps.

If they suspect testicular cancer, they may recommend additional tests to make an official diagnosis.

**What tests will be done to diagnose seminoma?**

A healthcare provider may recommend one or more of the following tests to diagnose seminoma:

* Testicular ultrasound.
* Other imaging tests.
* Serum tumor marker test.
* Orchiectomy.

After diagnosing seminoma, a provider will use cancer staging to determine the size of your tumor and if it has spread to other areas of your body.

Testicular ultrasound

A testicular ultrasound is a noninvasive imaging test that uses sound waves to show real-time images or video of your testicles.

Other imaging tests

A CT scan (computed tomography scan), X-ray or MRI (magnetic resonance imaging) can determine if testicular cancer has spread to other areas of your body.

Serum tumor marker test

This is a type of blood test that looks for tumor markers. Tumor markers are substances that cancer cells make, or that healthy cells make in response to cancer. A serum tumor marker test will look for the substances alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (beta-HCG) and lactate dehydrogenase (LDH). Different types of testicular cancers will produce different types and quantities of tumor markers. Having negative tumor markers also doesn’t rule out the presence of testicular cancer. Some tumors don’t make any tumor markers.

Orchiectomy

A surgeon will remove your affected testicle and send it to a pathologist to examine it for cancer cells. Providers use an orchiectomy to both diagnose and treat seminoma.

**Stages of seminoma**

Healthcare providers stage testicular cancer from 0 to 3 for seminomas and non-seminomas. Non-seminomas are another type of testicular germ cell tumor. They grow larger and spread faster than seminomas. Unlike other types of cancer, there isn’t a stage 4. In general, the lower the stage number, the slower the cancer grows. Stages 1 through 3 also have substages (A, B, C or S) to go into more detail.

Providers may also use the TNM system to provide further detail:

* Tumor (T). The size of the tumor and whether it has spread to nearby areas.
* Node (N). Whether cancer has spread to nearby lymph nodes or your abdomen.
* Metastasis (M). Whether cancer has spread to distant parts of your body.
* Serum tumor markers (S). Whether blood tests indicate high tumor marker levels.

This information can be confusing or even overwhelming. But it’s essential information for your providers to diagnose and plan your treatment.

**Management and Treatment**

For all seminoma stages, healthcare providers recommend a radical inguinal orchiectomy. During a radical inguinal orchiectomy, a surgeon removes your affected testicle(s) and spermatic cord. Your spermatic cord carries semen from your testicles to your penis during ejaculation. It also supplies blood to your testicles and contains nerves, lymph vessels and the vas deferens. The surgeon will close off the blood vessels and lymphatic vessels to prevent cancer from spreading to other areas.

Other seminoma treatments depend on your cancer staging after a radical inguinal orchiectomy. They may involve one or more of the following:

* Active surveillance. A provider may recommend active surveillance after a radical inguinal orchiectomy to treat early-stage seminoma. It involves regular monitoring and tests to see if seminoma spreads.
* Chemotherapy. Chemotherapy uses medicines to destroy cancer cells.
* Radiation therapy (radiotherapy). Radiation therapy uses high-powered X-rays to destroy cancer cells.

**Outlook / Prognosis**

The outlook for seminoma is very good. It’s usually very treatable:

* The overall survival rate is higher than 95%.
* The survival rate is 99% with early diagnosis and if the cancer doesn’t spread beyond your testicle.
* The survival rate is 96% if it spreads to nearby lymph nodes.
* The survival rate is over 70% even if it affects other areas of your body.

After seminoma treatment, you’ll need regular checkups for the rest of your life to make sure cancer doesn’t come back. Your checkups may include:

* Physical examination of your unaffected testicle (contralateral testicle).
* Regular blood tests for tumor markers.
* Periodic X-rays or CT scans.

**What is the mortality rate for seminoma?**

Even though seminoma is usually treatable, there’s still a small chance it could be fatal. According to the American Cancer Society, about 1 in 5,000 cases of testicular cancer is fatal.

**Prevention**

You can’t prevent seminoma. But it’s a good idea to perform monthly testicular self-exams to help keep track of any changes to the look and feel of your testicles. Schedule an appointment with a healthcare provider if you notice any lumps or size changes.

You may also be able to lower your overall cancer risk by:

* Quitting smoking and vaping.
* Getting 20 to 30 minutes of physical activity each day.
* Eating lots of fruits, vegetables and whole grains.
* Limiting how much alcohol you drink.
* Maintaining a healthy weight for you.

**Living With**

Even though seminoma has a very good outlook, finding out you have testicular cancer can stir many different feelings. Whatever you’re feeling is perfectly OK. Some days you may feel confident. Other days you may feel angry or frustrated. It’s important to take the time you need to process your feelings. The following tips may help:

* Make sure to rest when you’re tired.
* Find a good way to manage your stress. This may include physical activity, yoga, meditation or art therapy.
* Look into cancer survivorship programs.
* Find a testicular cancer support group.
* Lean on your family or close friends for support.

**When should I see a healthcare provider?**

Schedule an appointment with a healthcare provider if you notice any lumps or other changes to your testicles. They can diagnose what kind of mass you have and, if necessary, recommend additional testing and treatment.

If you receive treatment for seminoma, be sure to schedule regular checkups with a provider to monitor your overall health and ensure it doesn’t return.

**What questions should I ask a healthcare provider?**

Has the cancer spread to other areas of my body?

After diagnosis, imaging tests such as CT scans and blood tumor markers help determine if seminoma has spread beyond the testicle. Most stage 1 seminomas are confined to the testicle. If spread occurs, it is often to lymph nodes in the abdomen or pelvis, and less commonly to distant organs.

Which treatments do you recommend?

* Stage 1 seminoma: The main treatment is radical inguinal orchiectomy (removal of the affected testicle and spermatic cord). After surgery, active surveillance with regular follow-up is preferred if you can comply with frequent monitoring.
* If surveillance is not feasible or if risk factors are present, radiation therapy to abdominal lymph nodes or a short course of chemotherapy (usually carboplatin) may be recommended.
* For relapsed or advanced seminoma, chemotherapy regimens such as BEP (bleomycin, etoposide, cisplatin) or salvage chemotherapy combinations are used. Surgery or radiation may also be options depending on disease location.

What are the benefits and risks of your recommended treatments?

* Surgery removes the tumor and provides diagnosis with relatively low risk.
* Active surveillance avoids immediate side effects but requires strict follow-up.
* Radiation therapy is effective but may increase the risk of secondary cancers and cause fatigue, nausea, or bowel symptoms.
* Chemotherapy is highly effective but can cause side effects like nausea, hair loss, fatigue, and long-term risks including infertility and secondary cancers.

How long will treatment take?

* Surgery is usually a one-day procedure with a few weeks of recovery.
* Active surveillance involves regular visits and tests over several years.
* Radiation therapy courses typically last 3–4 weeks.
* Chemotherapy regimens usually last 3–4 months depending on the number of cycles.

Can I still have biological children?

* Many men retain fertility after treatment, especially if only one testicle is removed.
* Chemotherapy and radiation can reduce fertility temporarily or permanently.
* Sperm banking before treatment is recommended if you wish to have children in the future.

Can I get a prosthetic testicle?

* Yes, a testicular prosthesis can be implanted during or after orchiectomy for cosmetic and psychological reasons.

What’s my outlook?

* Seminoma has an excellent prognosis.
* The overall survival rate is higher than 95%, with early-stage disease having a near 99% cure rate.
* Even advanced or relapsed seminoma is highly treatable with current therapies.

**What is worse seminoma or non-seminoma?**

Seminoma tumors usually respond to treatment better than non-seminoma tumors. Non-seminoma tumors consist of more than one type of cell and usually grow faster than seminoma tumors.

**DIFFERENTIAL DIAGNOSIS**

Histological differential diagnosis of seminoma include:

* Non-seminomatous germ cell tumor, including embryonal carcinoma, cholangiocarcinoma, yolk sac tumor or teratoma
* Leydig and Sertoli cell tumors
* Granulosa cell tumors
* Gonadoblastoma
* Lymphoma
* Mesothelioma
* Adenocarcinoma of the rete testis
* Epidermoid cyst
* Metastatic carcinoma
* Epididymitis
* Hydrocele

**EPIDEMIOLOGY**

Testicular germ cell tumors (GCTs) account for the most common malignancy in men aged 15 to 34 years. However, it accounts for less than 1% of all male tumors. The incidence of testicular tumors is rising from the past 20 years. In the United States, testicular seminoma is the most common subtype of testicular cancer.A higher incidence of seminoma is seen among Whites than in African Americans, and the rate has increased in the White population over recent decades

**Common Chemotherapy Drugs Used for Seminoma**

1. BEP regimen (most common for advanced or metastatic seminoma)
2. Bleomycin
3. Etoposide
4. Cisplatin
5. Carboplatin (often used as single-agent chemotherapy for stage 1 seminoma or adjuvant therapy)
6. EP regimen (Etoposide + Cisplatin), used in some cases to avoid bleomycin toxicity

Side Effects of Seminoma Chemotherapy Drugs

| Drug | Common Side Effects | Serious or Long-Term Risks |
| --- | --- | --- |
| Bleomycin | Fatigue, fever, skin rash | Lung toxicity (pulmonary fibrosis causing shortness of breath) |
| Etoposide | Nausea, vomiting, hair loss, mouth sores, fatigue | Low blood counts increasing infection risk, secondary leukemia (rare) |
| Cisplatin | Nausea, vomiting, hair loss, neuropathy (tingling/numbness in hands and feet), kidney damage, hearing loss (ototoxicity) | Permanent nerve damage, kidney impairment, hearing loss |
| Carboplatin | Nausea, vomiting, fatigue, low blood counts | Kidney damage (less than cisplatin), neuropathy (less common) |

**General Side Effects of Chemotherapy for Seminoma**

* Nausea and vomiting: Often managed with anti-nausea medications.
* Fatigue: Common during and after treatment.
* Hair loss: Usually starts about 3 weeks into treatment; typically temporary.
* Mouth sores: Painful ulcers in the mouth and throat.
* Diarrhea or constipation: Gastrointestinal upset is common.
* Increased risk of infection: Due to low white blood cell counts from bone marrow suppression.
* Easy bruising or bleeding: From low platelet counts.
* Loss of appetite and weight changes.
* Neuropathy: Tingling or numbness in fingers and toes, sometimes persisting months after treatment.
* Kidney damage: Particularly with cisplatin, mitigated by hydration protocols.
* Hearing loss: Cisplatin can cause tinnitus and permanent hearing loss.
* Lung toxicity: Bleomycin can cause lung damage, requiring monitoring with lung function tests.

Fertility Considerations

* Chemotherapy can reduce fertility temporarily or permanently.
* About 30% of men may remain infertile after chemotherapy.
* Sperm banking before treatment is strongly recommended.

Duration of Treatment

* Chemotherapy courses typically last 3 to 4 months, depending on the stage and regimen.
* Radiation therapy (if used) usually lasts 3 to 4 weeks.

**Genomic Features of Seminoma**

* KIT mutations are among the most frequent somatic mutations in seminomas, found in approximately 6–19% of cases. KIT encodes a receptor tyrosine kinase important in germ cell development, and its mutation contributes to tumorigenesis in seminoma.
* RAS family mutations (KRAS, NRAS, HRAS) occur less commonly but are present in some seminomas, activating pathways involved in cell proliferation.
* TP53 mutations are relatively uncommon in seminomas compared to other cancers but have been reported in a minority of cases.
* Other genes occasionally mutated include BRAF, FGFR3, PTEN, SMAD4, and STK11 (the latter associated with hereditary cancer syndromes like Peutz-Jeghers syndrome).

Genetic Risk and Inheritance

* Nearly half (about 49%) of the risk for developing testicular germ cell tumors (including seminoma) is estimated to come from inherited genetic factors, which is higher than for most other cancers.
* This inherited risk arises from the combined effect of many common genetic variants (single nucleotide polymorphisms or SNPs), rather than a single high-impact mutation.
* The KIT ligand gene (KITLG) is a prominent susceptibility gene, with certain alleles increasing risk by more than twofold. KITLG interacts with KIT, reinforcing the biological importance of this pathway in seminoma.
* Genome-wide association studies (GWAS) have identified about 50 SNPs linked to testicular cancer risk, implicating pathways involved in germ cell development, telomerase function, microtubule assembly, and DNA repair.
* Familial testicular cancer is rare but recognized, and mutations in genes such as CHEK2 and STK11 may contribute to hereditary risk

**DOCTOR PATIENT CONVERSATION**

Doctor: Hello, I want to talk with you about your diagnosis. The tests show you have seminoma, a type of testicular cancer. It’s usually very treatable, especially when caught early.

Patient: What exactly is seminoma? How serious is it?

Doctor: Seminoma is a cancer that starts in the germ cells of the testicle. It tends to grow slowly and responds well to treatment. Most men with early-stage seminoma have an excellent prognosis.

Patient: Has the cancer spread beyond my testicle?

Doctor: We’ve done imaging and blood tests, and it appears your cancer is localized to the testicle, which is stage 1. That means it hasn’t spread to lymph nodes or other organs.

Patient: What treatment do you recommend?

Doctor: The first step is surgery to remove the affected testicle, called an orchiectomy. After that, depending on your risk factors and preferences, we might recommend either active surveillance, a single dose of chemotherapy (carboplatin), or radiation therapy to reduce the chance of recurrence.

Patient: What are the benefits and risks of these treatments?

Doctor: Surgery removes the tumor and is the main treatment. Active surveillance avoids immediate side effects but requires regular follow-up. Chemotherapy and radiation are effective at preventing recurrence but can have side effects like fatigue, nausea, or risk of secondary cancers, though these are generally low with modern protocols.

Patient: How long will treatment and recovery take?

Doctor: Surgery is usually a day procedure with a few weeks of recovery. Chemotherapy or radiation, if needed, typically take a few weeks. Active surveillance means regular check-ups for several years.

Patient: Will I still be able to have children?

Doctor: Many men retain fertility with one testicle. However, chemotherapy or radiation can affect fertility, so sperm banking before treatment is often recommended.

Patient: Can I get a prosthetic testicle?

Doctor: Yes, you can choose to have a testicular prosthesis implanted during or after surgery for cosmetic and psychological reasons.

Patient: What is my outlook?

Doctor: Seminoma has a very high cure rate, over 95%, especially at early stages like yours. We will monitor you closely to catch any recurrence early.

Patient: What kind of follow-up will I need?

Doctor: Regular visits with physical exams, blood tests for tumor markers, and imaging as needed, usually every few months initially, then less frequently over time.

Patient: Thank you. This helps me understand what to expect.

Doctor: You’re welcome. Please feel free to ask any questions anytime. We’re here to support you through this.

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**Leiomyosarcoma**

Leiomyosarcoma (LMS) is a rare, aggressive cancer that forms in smooth muscles. Smooth muscles are involuntary muscles located in various parts of your body. You have smooth muscles in your hollow organs, including your:

* Bladder
* Blood vessels
* Large intestine
* Small intestine
* Stomach
* Uterus

LMS cancer is a type of soft tissue sarcoma. It grows quickly and can double in size in as little as one month. The cancer cells travel through your bloodstream and can spread to any soft tissue in your body.

Some people don’t develop LMS symptoms until the disease reaches an advanced stage. In these cases, leiomyosarcoma is life-threatening. But when it’s detected and treated early, recovery is possible.

A cancer diagnosis can be overwhelming. Lean on your healthcare team. They can recommend resources and support groups that may help you on your journey.

**Types of leiomyosarcoma**

There are three subtypes of leiomyosarcoma:

* Somatic soft tissue LMS. This affects your connective tissue. It’s the most common form of LMS. Uterine leiomyosarcoma is one example of somatic soft tissue LMS.
* Cutaneous or subcutaneous LMS. This involves piloerector muscles in your skin and eyes. Your piloerector muscles give your skin goosebumps and make your pupils dilate.
* LMS of a vascular origin. This forms in a major blood vessel, like your pulmonary arteries, inferior vena cava or peripheral arteries. It’s the rarest form of LMS.

In the United States, about 15,000 people receive a soft tissue sarcoma diagnosis every year. Leiomyosarcoma accounts for 10% to 20% of those cases. About 1 in every 100,000 people in the U.S. develops LMS cancer.

Leiomyosarcoma can affect anyone. But it’s most common in females over age 5.

**Symptoms and Causes**

Leiomyosarcoma symptoms vary depending on the size and location of the tumor. Some people don’t experience symptoms early on, but may notice certain signs as the tumor grows, like:

* A firm, painless lump
* Abdominal bloating
* Fever
* Nausea and vomiting
* Pain
* Tiredness
* Weight loss

Leiomyosarcoma in your digestive system may cause:

* Abdominal pain
* Black stools (from blood in your poop)
* Loss of appetite
* Nausea and vomiting

Uterine leiomyosarcoma can cause:

* Abnormal uterine bleeding
* Frequent urination
* Vaginal discharge

**What causes leiomyosarcoma?**

Experts aren’t exactly sure what causes leiomyosarcoma. It could be hereditary (meaning you inherited altered genes from your parents), or it could be because your own genes changed, causing normal cells to grow out of control and become cancer cells.

Researchers have found links between LMS and these genetic conditions:

* Gardner syndrome
* Gorlin syndrome
* Hereditary retinoblastoma
* Li-Fraumeni syndrome
* Neurofibromatosis type 1 (NF1)
* Tuberous sclerosis
* Werner syndrome

**Diagnosis and Tests**

A healthcare provider will do a physical examination and ask you about your symptoms. They’ll also review your medical history, including any past or current health conditions.

Your provider will take imaging tests to see inside your body and determine the size and location of the tumor. These imaging tests may include:

* Angiography
* Computed tomography (CT) scans
* Magnetic resonance imaging (MRI)
* PET scan

Your provider will likely need to do a biopsy, too. When testing for LMS, providers try to take small samples from several parts of the cancer. Once they have the tissue samples, they’ll send them to a pathologist for testing.

**Management and Treatment**

Leiomyosarcoma treatment depends on the location and size of the tumor. Options include:

* Surgery. When surgery is possible, it’s the go-to treatment option for leiomyosarcoma. The goal is to remove the entire tumor so that the cancer doesn’t come back.
* Chemotherapy. Providers recommend chemotherapy when the tumor is large, or when cancer cells have spread to other parts of your body.
* Radiation therapy. Providers might use radiation therapy before surgery (neoadjuvant therapy) to shrink the tumor, or after surgery (adjuvant therapy) to kill any remaining cancer cells.
* Targeted therapy. Your healthcare team may recommend targeted therapy as a stand-alone therapy or in combination with other treatments.

**How long does it take to recover from leiomyosarcoma treatment?**

Recovery times can vary drastically depending on several factors, including:

* The size and location of the cancer
* The type of treatment you receive
* Your body’s healing capacity

It could take several weeks or months to fully recover. Even after you’re feeling better, you’ll still need regular checkups to monitor your health and reduce the risk of cancer recurrence (return).

**Outlook / Prognosis**

The outlook for leiomyosarcoma varies significantly depending on the stage, size and location of the tumor. In some cases, LMS is curable, especially when detected and treated early.

Treatment is more complicated when it’s discovered in the later stages. Advanced, Stage 4 leiomyosarcoma can be managed with treatment, but not cured.

**What is the survival rate of leiomyosarcoma?**

Leiomyosarcoma survival rates depend on several factors like:

* Tumor size and location
* How much of the tumor your surgeon can remove
* Whether the cancer has spread — and if so, how far

The following shows five-year survival rates for three different stages of LMS (localized, regional and distant):

| **Cancer stage** | **Description** | **Five-year survival rate** | **What this means** |
| --- | --- | --- | --- |
| Localized | Cancer hasn’t spread beyond where it started. | 63% | Sixty-three of 100 people with localized LMS will still be alive five years after their diagnosis. |
| Regional | Cancer has spread to surrounding tissues and possibly to nearby lymph nodes. | 36% | Thirty-six out of 100 people with regional LMS will still be alive five years after their diagnosis. |
| Distant | Cancer has spread to distant areas of your body. | 14% | Fourteen out of 100 people with distant LMS will still be alive five years after their diagnosis. |

Survival rates are only estimates. Researchers base them on the experiences of people who had LMS in the past. Survival rates can’t tell you how long you’ll live or how well you’ll respond to treatment.

To learn more about survival rates and what they mean for you, talk to your healthcare provider.

**Prevention**

Currently, there’s no known way to prevent leiomyosarcoma. But you can reduce your risk by avoiding risk factors whenever possible. Known leiomyosarcoma risk factors include:

* Certain viral infections, like human herpesvirus 8 (HHV8)
* Radiation exposure
* Tamoxifen (commonly used to treat breast cancer)

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

If you’re undergoing treatment for leiomyosarcoma, call your healthcare provider whenever you notice new or worsening symptoms. For example, if you notice any changes to your tumor — or if you develop severe pain, sudden weight changes or other symptoms — seek prompt medical care.

**DIFFERENTIAL DIAGNOSIS**

The clinical presentation of a patient with STS is vague and nonspecific. The morphological diagnosis based on microscopic examination remains the gold standard. Ancillary testing, including immunohistochemistry, classical cytogenetics, and molecular testing, aids in diagnosis. The World Health Organization (WHO) recognizes more than 70 different subtypes of sarcoma. Diagnoses to consider due to similar presentation or histopathological similarity include meningioma, gastrointestinal stromal tumors, leiomyoma, dedifferentiated liposarcoma, endometrial stromal sarcoma, STUMP, inflammatory myofibroblastic tumor, and perivascular epithelioid cell tumor.

**EPIDEMIOLOGY**

Leiomyosarcoma accounts for 10% to 20% of all newly diagnosed STS. In recent years, advancements in molecular diagnostics have enhanced the accuracy of diagnosis. Leiomyosarcoma most commonly occurs in the retroperitoneum, followed by the uterus, extremities, and trunk. Uterine sarcomas comprise about 3% to 7% of all uterine malignancies, with leiomyosarcoma being the most common subtype, accounting for nearly 80% of all uterine sarcomas.

The incidence of leiomyosarcoma increases with age, reaching its peak in the seventh decade of life. The exception to this is uterine leiomyosarcoma, which occurs most commonly in perimenopausal women. Tumors associated with genetic syndromes occur earlier in life. Retroperitoneal leiomyosarcoma and tumors arising from visceral blood vessels are more common in women, whereas the disease at other sites is more common in men

**Common Chemotherapy Drugs for Leiomyosarcoma**

1. Doxorubicin
2. Often used as first-line chemotherapy, either alone or in combination.
3. Can be combined with trabectedin for improved survival in advanced/metastatic LMS.
4. Combination regimens with ifosfamide, gemcitabine + docetaxel, or olaratumab have also been studied.
5. Trabectedin (Yondelis)
6. Used in combination with doxorubicin or as maintenance therapy after initial chemotherapy.
7. Approved for advanced or unresectable LMS.
8. Gemcitabine + Docetaxel
9. Common second-line regimen with synergistic effects.
10. Used especially in uterine LMS and other soft tissue sarcomas.
11. Ifosfamide
12. Sometimes combined with doxorubicin for enhanced effect but with increased toxicity.
13. Targeted therapies and novel agents (under investigation)
14. PARP inhibitors (e.g., olaparib) targeting DNA repair pathways.
15. Immunotherapy combinations and metabolic pathway inhibitors are emerging.

Side Effects of Leiomyosarcoma Chemotherapy Drugs

| Drug | Common Side Effects | Serious or Long-Term Risks |
| --- | --- | --- |
| Doxorubicin | Nausea, vomiting, hair loss, fatigue, mouth sores | Cardiotoxicity (heart damage), myelosuppression, secondary leukemia (rare) |
| Trabectedin | Fatigue, nausea, vomiting, liver enzyme elevation | Myelosuppression, rhabdomyolysis (muscle breakdown), hepatotoxicity |
| Gemcitabine | Flu-like symptoms, rash, nausea, fatigue | Myelosuppression, liver toxicity |
| Docetaxel | Fluid retention, neuropathy, nail changes, fatigue | Myelosuppression, hypersensitivity reactions |
| Ifosfamide | Nausea, vomiting, fatigue, hemorrhagic cystitis | Neurotoxicity, nephrotoxicity, myelosuppression |

**Treatment Overview and Considerations**

* Surgery remains the primary treatment for localized LMS, aiming for complete resection with clear margins.
* Radiation therapy may be used pre- or post-operatively to reduce local recurrence risk, especially in high-grade tumors.
* Chemotherapy is mainly reserved for advanced, metastatic, or unresectable LMS due to relative resistance to standard agents.
* Combination chemotherapy regimens improve response rates and progression-free survival but have modest impact on overall survival.
* Recent phase III trials show that adding trabectedin to doxorubicin improves overall survival compared to doxorubicin alone in advanced LMS.
* Molecular profiling is increasingly guiding novel targeted therapies and clinical trial enrollment.

**Genomic Alterations in Leiomyosarcoma**

* Tumor Suppressor Gene Mutations:
* RB1 mutations or deletions are highly prevalent, observed in approximately 50–90% of LMS cases across soft tissue, uterine, and cutaneous subtypes. RB1 loss is a major driver of LMS pathogenesis.
* TP53 mutations occur in about 30–60% of LMS tumors and are associated with aggressive behavior and poor prognosis.
* PTEN mutations or deletions are seen in roughly 30% of LMS, contributing to dysregulated PI3K/AKT/mTOR signaling.
* Chromatin Remodeling and DNA Repair Genes:
* Mutations in ATRX and DAXX (involved in chromatin remodeling and telomere maintenance) are frequent, especially in uterine LMS (about 50% ATRX mutations). These mutations correlate with alternative lengthening of telomeres (ALT) and worse survival.
* Some LMS tumors show signatures of homologous recombination deficiency (HRD), including mutations in BRCA2 and other DNA repair genes, suggesting potential sensitivity to PARP inhibitors.
* Copy Number Variations (CNVs):
* Recurrent copy number losses include regions containing RB1, PTEN, CYLD, and others.
* Amplifications have been identified in oncogenes such as MYOCD, IGF1R, C-MYC, and MAP2K4.
* Mutational Signatures and Etiology:
* Cutaneous LMS shows UV-related mutational signatures (SBS7a/b), implicating ultraviolet light exposure in pathogenesis.
* Uterine LMS exhibits complex genomic rearrangements including chromoplexy and chromothripsis.
* Fusion Genes:
* Rare recurrent fusions such as CRTC1/CRTC3::MAML2 have been reported in cutaneous LMS, with novel fusions identified in individual cases.
* Genomic Risk Stratification:
* Recent studies propose genomic risk models incorporating mutations like ATRX and others to better predict progression-free and overall survival, especially in soft tissue LMS where traditional clinical factors like tumor size may be less predictive.

**What questions should I ask my doctor?**

If you have leiomyosarcoma, talking with your healthcare provider can inform, empower and help you take control of your health. Here are some questions you may want to ask:

Where’s my cancer located?

Leiomyosarcoma is a cancer of smooth muscle cells and can arise anywhere in the body where smooth muscle is present. Common sites include the uterus, abdomen/retroperitoneum, blood vessels, and extremities. Imaging studies (MRI, CT scans) and biopsy help determine the exact tumor location.

Has my cancer spread?

Leiomyosarcoma can spread locally and metastasize, most commonly to the lungs, liver, and bones. Staging scans assess whether the cancer is:

* Localized (confined to the original site),
* Regional (spread to nearby tissues or lymph nodes), or
* Distant (spread to distant organs).

How advanced is my cancer?

The stage depends on tumor size, location, and spread:

* Localized LMS: Tumor confined to origin site.
* Regional LMS: Spread to nearby tissues or lymph nodes.
* Distant LMS: Metastasis to distant organs.

Survival rates vary by stage:

* Localized: ~63% 5-year survival
* Regional: ~36% 5-year survival
* Distant: ~14% 5-year survival

What are my treatment options?

* Surgery is the primary treatment for localized LMS, aiming for complete tumor removal with clear margins.
* Radiation therapy may be used before or after surgery to reduce recurrence risk.
* Chemotherapy is used for advanced, metastatic, or unresectable LMS. Common drugs include doxorubicin, trabectedin, and gemcitabine + docetaxel.
* Treatment plans are individualized based on tumor location, size, grade, and patient health.

What are the risks and side effects of treatment?

* Surgery risks depend on tumor location and extent; may include bleeding, infection, or functional loss.
* Radiation therapy can cause fatigue, skin changes, and localized tissue effects.
* Chemotherapy side effects vary by drug but commonly include nausea, fatigue, hair loss, low blood counts, neuropathy, and potential organ toxicities (heart, liver, kidneys).
* Your care team will monitor and manage side effects closely.

What are the chances that my cancer will come back after treatment?

Leiomyosarcoma has a high risk of recurrence, especially in high-grade or large tumors. Even after complete resection, close follow-up is critical to detect and treat recurrences early.

What’s my outlook?

Prognosis depends on stage, tumor grade, size, and response to treatment:

* Localized LMS has a 5-year survival rate around 63%.
* Regional spread lowers 5-year survival to about 36%.
* Distant metastases reduce survival to approximately 14% at 5 years.

**Doctor-patient conversation about Leiomyosarcoma**

Doctor:  
"Thank you for coming in today. I want to talk with you about the results of your biopsy. The diagnosis is leiomyosarcoma, which is a type of cancer that arises from smooth muscle cells. It’s a rare and sometimes aggressive tumor, but there are treatment options we can discuss."

Patient:  
"I’m really worried. What does this mean for me? What kind of treatments are available?"

Doctor:  
"I understand this is overwhelming news. Leiomyosarcoma can behave differently depending on its size, location, and whether it has spread. Treatment usually involves surgery to remove the tumor, and sometimes radiation or chemotherapy might be needed depending on the case."

Patient:  
"Will I need to see a specialist?"

Doctor:  
"Yes, I recommend you see a sarcoma specialist—a doctor who has experience treating leiomyosarcoma and other soft tissue sarcomas. I will refer you to one, and we can work together with them to develop the best treatment plan for you. If you want, you can also get a second opinion from another sarcoma expert."

Patient:  
"That sounds good. Will I be able to get treatment close to home?"

Doctor:  
"Often, the sarcoma specialist can coordinate with your local doctors so that some treatments can be done near your home. We will make sure you have support throughout your care."

Patient:  
"What should I do next?"

Doctor:  
"I suggest you take some time to process this information. It might help to write down any questions or concerns you have, and bring a family member or friend to your next appointment. We can also provide you with educational materials about leiomyosarcoma and connect you with support groups."

Patient:  
"Thank you. I appreciate you explaining everything clearly."

Doctor:  
"Of course. Remember, we’re here to support you every step of the way. If you have questions before your next visit, please don’t hesitate to contact me."

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**RHABDOMYOSARCOMA**

**DEFINITION AND DESCRIPTION**

Rhabdomyosarcoma is a rare type of cancer that starts as a growth of cells in soft tissue. Soft tissues support and connect organs and other parts of the body. Rhabdomyosarcoma most often starts in muscle tissue.

Although rhabdomyosarcoma can start anywhere in the body, it's more likely to start in the:

* Head and neck area.
* Urinary system, such as the bladder.
* Reproductive system, such as the vagina, uterus and testes.
* Arms and legs.

Rhabdomyosarcoma treatment often involves surgery, chemotherapy and radiation therapy. Treatment depends on where the cancer starts, how large it grows and whether it spreads to other parts of the body.

Research into diagnosis and treatment have greatly improved the outlook for people diagnosed with rhabdomyosarcoma. More and more people are living for years after a rhabdomyosarcoma diagnosis.

**Symptoms**

Signs and symptoms of rhabdomyosarcoma depend on where the cancer starts.

For example, if the cancer is in the head or neck area, symptoms may include:

* Headache.
* Bleeding in the nose, throat or ears.
* Tearing, bulging or swelling of the eyes.

If the cancer is in the urinary or reproductive system, symptoms may include:

* A mass or bleeding in the vagina or rectum.
* Trouble urinating and blood in the urine.
* Trouble with bowel movements.

If the cancer is in the arms or legs, symptoms may include:

* Possibly pain in the affected area, if the cancer pushes on nerves or other areas of the body.
* Swelling or a lump in the arm or leg.

**Causes**

It's not clear what causes rhabdomyosarcoma. It starts when a soft tissue cell develops changes in its DNA. A cell's DNA holds the instructions 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**

Factors that may increase the risk of rhabdomyosarcoma include:

* **Younger age.** Rhabdomyosarcoma most often happens to children younger than 10.
* **Inherited syndromes.** Rarely, rhabdomyosarcoma has been linked to genetic syndromes that are passed from parents to children. These include neurofibromatosis 1, Noonan syndrome, Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome and Costello syndrome.

There is no way to prevent rhabdomyosarcoma.

**Complications**

Complications of rhabdomyosarcoma and its treatment include:

* **Cancer that spreads.** Rhabdomyosarcoma can spread from where it started to other parts of the body. When cancer spreads, it might require more-intense treatments. This can make recovery harder. Rhabdomyosarcoma most often spreads to the lungs, lymph nodes and bones.
* **Long-term side effects.** Rhabdomyosarcoma and its treatments can cause many side effects, both short and long term. Your healthcare team can help you manage the side effects that happen during treatment. And the team can give you a list of side effects to watch for in the years after treatment.

**Diagnosis**

Rhabdomyosarcoma diagnosis usually begins with a physical exam. Based on the results, the healthcare team might recommend other tests. These may include imaging tests and a procedure to remove a sample of cells for testing.

**Imaging tests**

Imaging tests make pictures of the inside of the body. They might help show the location and size of a rhabdomyosarcoma. Tests might include:

* X-rays.
* CT scans.
* MRI scans.
* Positron emission tomography scans, also called PET scans.
* Bone scans.

**Removing a sample of tissue for testing**

A biopsy is a procedure to remove a sample of tissue for testing in a lab. A biopsy for rhabdomyosarcoma needs to be done in a way that won't cause problems with future surgery. For this reason, it's a good idea to seek care at a medical center that sees many people with this type of cancer. Experienced healthcare teams will select the best type of biopsy.

Types of biopsy procedures used to diagnose rhabdomyosarcoma include:

* **Needle biopsy.** This method uses a needle to remove tissue samples from the cancer.
* **Surgical biopsy.** Sometimes, surgery might be needed to remove a larger sample of tissue.

The biopsy sample goes to a lab for testing. Doctors who study blood and body tissue, called pathologists, will test the cells for cancer. Other special tests give more details about the cancer cells. Your healthcare team uses this information to make a treatment plan.

**Treatment**

Rhabdomyosarcoma treatment most often combines chemotherapy, surgery and radiation therapy.

Which treatments your healthcare team suggests depends on where the cancer is and the size of the cancer. Treatment also will depend on how fast the cancer cells are likely to grow and whether the cancer has spread to other parts of the body.

**Surgery**

The goal of surgery is to remove all the cancer cells. But that's not always possible if the rhabdomyosarcoma has grown around or near organs. If the surgeon can't safely remove all the cancer, your healthcare team will use other treatments to kill cancer cells that might be left. This might include chemotherapy and radiation.

**Chemotherapy**

Chemotherapy treats cancer with strong medicines. Many chemotherapy medicines exist. Treatment often involves a combination of medicines. Most chemotherapy medicines are given through a vein. Some come in pill form.

For rhabdomyosarcoma, chemotherapy is often used after surgery or radiation therapy. It can help kill cancer cells that might be left. Chemotherapy also can be used before other treatments. The chemotherapy can help shrink a cancer to make it easier to do surgery or radiation therapy.

**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 you. The machine directs radiation to precise points on your body.

For rhabdomyosarcoma, radiation therapy might be recommended after surgery. It can help kill cancer cells that might be left. Radiation therapy also can be used instead of surgery. Radiation therapy might be preferred if the cancer is in an area where surgery isn't possible because of nearby organs.

**Outlook / Prognosis**

Sometimes, treatment can cure rhabdomyosarcoma. This is called remission, which means that you don’t have symptoms and tests don’t detect signs of cancer. In many cases, remission is permanent, but rhabdomyosarcoma can come back. In general, adults are less likely to be cured than children.

**What is the life expectancy for someone with rhabdomyosarcoma?**

There’s no data on how long someone with rhabdomyosarcoma can expect to live. Researchers do track the percentage of people who were alive five years after receiving a diagnosis of rhabdomyosarcoma.

Survival rates vary widely depending on factors like the type of rhabdomyosarcoma, risk group classification and whether the condition comes back after treatment. Overall, 70% of children with this condition were alive five years after diagnosis. The five-year survival rate for adults is 20%.

Regardless of your situation, it’s important to remember that survival rates are estimates based on the experiences of other people who receive treatment for rhabdomyosarcoma. If you or your child have this condition, it’s understandable that you may want to know what to expect. If that’s your situation, your oncology team is your best resource for information.

**Living With**

Cancer disrupts your daily life, and rhabdomyosarcoma is no exception. If you or your child have this condition, you may feel overwhelmed and under stress. Here are some suggestions that may help:

* **Consider palliative care:** Cancer symptoms and cancer treatment can be tough to handle. Palliative care is a type of treatment that focuses on quality of life, from easing symptoms to finding mental health support.
* **Talk to a child life specialist:** Cancer upends children’s lives, taking them away from their friends and activities. Having cancer can be lonely for a child who’s going through something their friends may not understand. Child life specialists are specially trained healthcare providers who help children cope with medical experiences.
* **Get some rest:** Cancer treatment — and caring for a child with cancer — can be exhausting. If you’re receiving treatment, try to rest whenever you need to, not just when you have time. If you’re caring for a child with rhabdomyosarcoma, talk to your healthcare provider about programs and services that provide respite care.
* **Consider cancer survivorship:** Rhabdomyosarcoma can come back after treatment. If you or your child are worried cancer will come back, ask your provider about cancer survivorship support.

**When should I contact my oncologist?**

If you or your child are receiving treatment, contact your oncologist if treatment side effects are stronger than you expect. Depending on your situation, your oncologist may have specific guidance on symptoms that could mean rhabdomyosarcoma is spreading or coming back. Don’t hesitate to contact them with your concerns.

**QUESTION AND ANSWERS SET**

What type of rhabdomyosarcoma do I have/does my child have?

Rhabdomyosarcoma has four main subtypes:

* Embryonal RMS (ERMS): Most common in children (60–70% of cases), often found in head/neck and genitourinary tract. Includes the botryoid variant, which has a good prognosis.
* Alveolar RMS (ARMS): More aggressive, often affects older children and teenagers, associated with specific gene fusions (PAX3/7-FOXO1).
* Spindle cell/sclerosing RMS: Rare, with intermediate prognosis, often in paratesticular region or head/neck.
* Pleomorphic RMS: Mostly in adults, rare in children, with poorer prognosis.

Genetic testing for fusion genes (e.g., PAX3/7-FOXO1) helps distinguish alveolar RMS from embryonal and guides risk stratification.

What is the risk group classification?

Risk groups are based on tumor subtype, location, size, stage, and presence of metastases:

* Low risk: Favorable histology (e.g., botryoid embryonal), localized tumors in favorable sites.
* Intermediate risk: Most embryonal RMS without metastasis, some alveolar RMS without metastasis.
* High risk: Metastatic disease or unfavorable histology (fusion-positive alveolar RMS).

This classification guides treatment intensity.

What treatments do you recommend?

Treatment usually involves a multimodal approach:

* Surgery: To remove as much tumor as possible without causing major functional loss.
* Chemotherapy: Multi-agent regimens (e.g., vincristine, actinomycin D, cyclophosphamide/ifosfamide) tailored by risk group.
* Radiation therapy: Used for residual disease or tumors in locations where surgery is limited.

Treatment protocols vary by subtype and risk group, often guided by cooperative group studies (e.g., Children’s Oncology Group).

What are treatment side effects?

Side effects depend on the drugs and radiation used but may include:

* Chemotherapy: Nausea, hair loss, low blood counts (infection risk), fatigue, mouth sores, potential long-term effects on fertility and organ function.
* Surgery: Risks depend on tumor location; may include functional impairments.
* Radiation: Skin irritation, fatigue, and possible late effects on growth and organ function in children.

Supportive care is essential to manage these effects.

Are we eligible for any clinical trials?

Eligibility depends on factors such as age, tumor subtype, stage, prior treatments, and geographic location. Many clinical trials are ongoing to improve outcomes, including novel chemotherapy combinations, targeted therapies, and immunotherapies. Your oncology team can help identify suitable trials.

What is my child’s prognosis?

Prognosis varies widely:

* Embryonal RMS (especially botryoid subtype) and localized disease: 5-year survival rates up to 70–90%.
* Alveolar RMS and metastatic disease: Lower survival rates, around 30–50% depending on extent.
* Early diagnosis and multimodal therapy improve outcomes.

What supportive care can you offer to help us?

* Symptom management: Pain control, nutritional support, infection prevention.
* Psychosocial support: Counseling, support groups, educational resources.
* Fertility preservation: Discussed before treatment starts if relevant.
* Rehabilitation services: Physical and occupational therapy as needed.
* Coordination of care: Multidisciplinary teams including oncologists, surgeons, radiation therapists, nurses, and social workers.

**DIFFERENTIAL DIAGNOSIS**

Other musculoskeletal neoplasms that should be excluded include:

* Ewing sarcoma
* Li-Fraumeni syndrome
* Lipomas
* Liposarcoma
* Lymphadenopathy
* Lymphoproliferative disorders
* Neurofibromatosis type 1
* Osteosarcoma
* Wilms tumor

**EPIDEMIOLOGY**

Rhabdomyosarcoma (RMS) is a rare condition making up 3% of all pediatric cancers. However, RMS is the most common childhood and adolescent soft tissue sarcoma, comprising 50% of soft tissue sarcomas in individuals younger than 20. In the US, there are approximately 350 newly diagnosed patients each year. All histological subtypes of RMS have also been shown to be significantly more prevalent in males. RMS has a much lower incidence in adults, accounting for approximately 1% of solid cancers.

Although the various subtypes of RMS can arise anywhere in the body, the embryonal histological type is the most common, and the head and neck is the most frequently involved area. RMS involving the extremities is more frequently observed with the alveolar subtype. The pleomorphic and alveolar subtypes have the highest rates of metastases and, consequently, the poorest prognosis compared to other histologic types. The most common metastatic sites include the lungs, bone marrow, and lymph nodes

**Common Chemotherapy Drugs Used in Rhabdomyosarcoma**

* Vincristine
* Actinomycin D (Dactinomycin)
* Cyclophosphamide or Ifosfamide
* Doxorubicin (used in some protocols)
* Other agents may be added depending on risk group and protocol.

General Side Effects of Chemotherapy

Chemotherapy targets rapidly dividing cells, affecting both cancer and some healthy cells, leading to common side effects such as:

* Hair loss
* Mouth sores
* Loss of appetite
* Nausea and vomiting
* Diarrhea or constipation
* Fatigue

Chemotherapy can also suppress bone marrow function, causing:

* Leukopenia (low white blood cells): Increased infection risk
* Thrombocytopenia (low platelets): Easy bruising or bleeding
* Anemia (low red blood cells): Fatigue and weakness

Most side effects improve after treatment ends, and supportive medications can help manage symptoms.

Drug-Specific Side Effects

* Cyclophosphamide and Ifosfamide:
* Can cause bladder irritation and bleeding (hemorrhagic cystitis); prevented with hydration and mesna.
* Potential to damage ovaries or testicles, affecting fertility.
* Vincristine:
* May cause peripheral neuropathy (tingling, numbness, weakness), sometimes leading to foot drop. Physical therapy and braces can help.
* Doxorubicin:
* Risk of cardiotoxicity (heart damage), requiring cardiac monitoring.
* Actinomycin D:
* Can cause nausea, vomiting, and mouth sores.

Long-Term and Late Effects

* Increased risk of secondary cancers, especially leukemia, years after treatment.
* Potential fertility issues due to chemotherapy or radiation.
* Possible heart problems (cardiomyopathy) after anthracycline use.
* Bone growth and dental problems if radiation affects growing tissues.
* Endocrine disorders, such as thyroid dysfunction, especially after radiation.

**key genomic alterations and mutated genes associated with rhabdomyosarcoma**

* PAX3-FOXO1 fusion gene (t(2;13)(q35;q14)) — characteristic of alveolar RMS
* PAX7-FOXO1 fusion gene (t(1;13)(p36;q14)) — variant fusion in alveolar RMS
* TP53 — tumor suppressor gene; mutations linked to worse prognosis in both fusion-positive and fusion-negative RMS
* MYOD1 — mutations associated with poor outcome, especially in spindle cell/sclerosing RMS
* RAS family genes (HRAS, NRAS, KRAS) — frequently mutated in fusion-negative RMS, especially in infants
* NF1 — tumor suppressor gene, often co-mutated with RAS pathway genes
* BCOR — mutated in a subset of fusion-negative RMS, linked to worse event-free survival
* FBXW7 — novel mutations identified, involved in protein degradation pathways
* PIK3CA — mutations affecting PI3K/AKT pathway
* FGFR4 — mutations contributing to oncogenic signaling
* CDKN2A — deletions or mutations, associated with aggressive disease
* ALK amplification and expression — potential therapeutic target in some RMS cases
* MYCN, MDM2, CDK4 — gene amplifications reported in some tumors
* CTNNB1 (β-catenin) — mutations occasionally observed
* IRS2 locus amplification — noted in fusion-positive tumors

**DOCTOR PATIENT CONVERSATION**

Doctor: Hello. I want to discuss the diagnosis and treatment plan for your child’s rhabdomyosarcoma.

Parent: Thank you, doctor. Can you explain what type of rhabdomyosarcoma my child has?

Doctor: Certainly. There are different subtypes of RMS. Your child has the [embryonal/alveolar/spindle cell] type, which we identified through biopsy and genetic testing. This helps us understand how aggressive the tumor might be and guides treatment.

Parent: How do you classify the risk group? What does that mean for treatment?

Doctor: We classify RMS into low, intermediate, or high risk based on tumor size, location, spread, and subtype. Your child falls into the [risk group], which means we will tailor treatment intensity accordingly to maximize effectiveness while minimizing side effects.

Parent: What treatments will my child need?

Doctor: Treatment usually involves a combination of surgery to remove the tumor, chemotherapy to target cancer cells throughout the body, and sometimes radiation therapy to treat any remaining tumor cells. The exact plan depends on the tumor’s size, location, and response to initial therapy.

Parent: What side effects should we expect from the treatment?

Doctor: Chemotherapy can cause side effects like hair loss, nausea, fatigue, and low blood counts, which increase infection risk. Surgery and radiation may have effects depending on the tumor location, such as temporary pain or long-term functional changes. We will provide supportive care to manage these side effects.

Parent: Are there any clinical trials my child could join?

Doctor: Yes, there are ongoing clinical trials testing newer drugs and treatment approaches. We can review eligibility criteria and see if any trials are suitable for your child’s situation.

Parent: What is my child’s prognosis?

Doctor: Prognosis varies by subtype and risk group. For example, children with embryonal RMS and localized disease have a 5-year survival rate of about 70–90%. We will do everything possible to achieve the best outcome.

Parent: What supportive care do you offer to help us through this?

Doctor: We have a multidisciplinary team including nurses, social workers, psychologists, and rehabilitation specialists to support you and your child emotionally and physically throughout treatment and recovery. We also provide resources for nutrition, pain management, and fertility preservation if needed.

Parent: Thank you, doctor. This helps us understand what to expect and how to prepare.

Doctor: You’re welcome. Please write down any questions as they come up. We’re here to support you every step of the way.

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**SYNOVIAL SARCOMA**

**DEFINITION AND DESCRIPTION**

Synovial sarcoma (synovial cell sarcoma) is a rare type of cancer that affects soft tissues, like your muscles or ligaments. It’s called synovial sarcoma because these cancer cells resemble the cells in your synovial joints (like your elbows, hips and shoulders).

Synovial sarcoma grows very slowly and may not cause pain. Many times, you won’t have symptoms until the tumor grows large enough to create a lump you can see and/or feel. Some people develop pain or numbness, especially if the tumor presses on nerves as it grows.

Early diagnosis and treatment are helping people with synovial sarcoma live longer, with hope for a cure. But a cancer diagnosis can turn your world upside down. What does this mean? What will my life look like now? If these are questions running through your mind, you’re not alone. Your healthcare team will walk with you every step of the way.

**Where does synovial sarcoma form?**

This type of cancer can affect several different areas of your body, including your abdomen, arms, feet, legs and lungs.

Synovial sarcoma can also form in joints like your:

* Ankles
* Elbows
* Hips
* Shoulders
* Wrists

Very rarely, synovial sarcoma can form in your chest, head or neck.

Like other soft tissue sarcomas, synovial sarcoma is an uncommon form of cancer. It affects about 1,000 people each year in the U.S. Anyone can get synovial sarcoma, but it’s most common in males under 30.

**Symptoms and Causes**

Synovial sarcoma cancer develops gradually over time. Tumors can grow undetected for up to two years. During this time, you may not have any symptoms at all. Once symptoms occur, they may include:

* A lump you can see and feel. (The lump might be painless.)
* Numbness
* Pain
* Swelling

Synovial sarcoma symptoms can look and feel like symptoms of other, less serious conditions like arthritis or bursitis. Because of this, synovial sarcoma may go undetected for a time. If you notice any kind of lump under your skin, schedule an appointment with a healthcare provider and see them as soon as possible.

**What causes synovial sarcoma?**

Researchers aren’t sure what causes synovial sarcoma. But they know it has something to do with mutations (changes) in your chromosomes. Synovial sarcoma cells always have one mutated gene in common. Sometimes, your chromosomes break into pieces. The pieces rejoin, but not in the same order or sequence.

Imagine your chromosome as a jigsaw puzzle and your genes as puzzle pieces. Now imagine someone jams a puzzle piece into a spot where it doesn’t belong. In synovial sarcoma, a gene called *SYT* jams up against genes that aren’t the right fit. When this happens, your cells don’t work as they should, and your body develops a mutant gene that causes synovial cell sarcoma.

**Diagnosis and Tests**

A healthcare provider will do a physical examination and ask you about your symptoms and health history. If they think you might have synovial cell sarcoma, they’ll refer you to an oncologist for further testing.

An oncologist will examine you and use imaging tests to see the size and location of the tumor.

Imaging tests might include:

* X-rays
* Magnetic resonance imaging (MRI)
* Ultrasound
* Computed tomography (CT) scan

Your provider will likely have the tumor biopsied. During this procedure, they’ll take a small tissue sample from the lump under your skin. Once they have the sample, they’ll send it to a pathologist, who will look at the cells under a microscope.

**Management and Treatment**

Surgery is the standard treatment for synovial sarcoma. The goal is to remove the tumor and some of the tissue around it to make sure it all comes out. In some cases, this means removing an entire muscle or muscle group. It depends on how far the cancer has spread. Your provider can tell you what to expect in your situation.

Providers may do surgery as a stand-alone treatment or in combination with other therapies like:

* Chemotherapy
* Radiation therapy
* Immunotherapy
* Targeted therapy
* Anti-angiogenesis drugs (which stop blood vessel formation and deprive cancer cells of the blood they need to survive)

Healthcare providers base treatment on several factors like tumor size and location, how long you’ve had the tumor and whether the cancer has spread (metastasized).

**Outlook / Prognosis**

Healthcare providers have made huge strides in treating synovial cell sarcoma. But there’s still a chance the condition will recur (return), sometimes, many years after treatment. You’ll likely have checkups for several years so your providers can monitor you closely.

**What’s the outlook for synovial sarcoma?**

The five-year survival rate for synovial sarcoma is 50% to 60%. That means that 5 to 6 out of 10 people with synovial sarcoma are still alive five years after their diagnosis.

The five-year metastasis-free survival rate is 40% to 60%. That means that within five years after treatment, cancer didn’t spread (metastasize) in 4 to 6 out of 10 people with synovial sarcoma.

Survival rates are only estimates and depend on several factors. Researchers base them on previous outcomes for other people diagnosed with the same condition. Survival rates can’t tell you how long you’ll live or how you’ll respond to a specific treatment. To learn more about survival rates — or to find out what they mean for your situation — talk to your healthcare provider.

**Prevention**

You can’t prevent synovial sarcoma because you can’t control the chromosomal changes that cause it.

You can lower your risk of metastasis (Stage 4 synovial sarcoma) with early detection and treatment. Stay aware of changes in your body. Tell a healthcare provider if you develop a lump that causes pain or doesn’t go away in a couple of weeks.

**Living With**

Cancer treatments for synovial sarcoma can take a toll on your body. The following can help boost your immune system and help you stay strong:

* **Ease your stress** with activities like meditation, mindfulness or relaxation exercises.
* **Get plenty of rest** and quality sleep.
* **Meet with a dietitian**, especially if cancer treatment causes appetite changes or changes to your sense of taste.
* **Reach out for support** from others who’ve been in your situation.
* **Try physical therapy** to regain your strength after surgery.

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

You’ll have regular visits with your healthcare provider during and after synovial sarcoma treatment. In addition, you should call your provider if you develop any new or worsening symptoms.

**What questions should I ask my doctor?**

You’ll have different questions during diagnosis, treatment and follow up. Some basic questions might be:

## **Where is my cancer located?**

Synovial sarcoma most commonly arises near the joints of the arms or legs but can occur anywhere in the body, including the pelvis, trunk, or head and neck. Imaging and biopsy determine the exact tumor location.

## **What caused my cancer?**

The exact cause of synovial sarcoma is unknown. It is linked to a specific genetic abnormality—a translocation between chromosomes 18 and X, creating the SS18-SSX fusion gene, which drives cancer development. There are no known lifestyle or environmental causes.

## **Has my cancer spread? If so, how far?**

Synovial sarcoma can spread (metastasize), most commonly to the lungs. The extent of spread is evaluated with imaging scans such as CT or PET scans. About 40–60% of patients remain metastasis-free five years after treatment.

## **What are my treatment options?**

* Surgery: The main treatment is surgical removal of the tumor with clear margins (1–3 cm if possible).
* Radiation therapy: Often given before or after surgery to shrink the tumor or kill remaining cancer cells.
* Chemotherapy: May be used before or after surgery, or for advanced disease.
* Targeted therapy and cell therapy: Newer options like afamitresgene autoleucel (Tecelra) are available for advanced cases.

Treatment plans depend on tumor size, location, and whether cancer has spread.

## **What are the possible side effects?**

* Surgery: Risks include pain, infection, possible loss of function depending on tumor location.
* Radiation: Fatigue, skin irritation, and potential long-term tissue changes.
* Chemotherapy: Nausea, hair loss, fatigue, low blood counts, increased infection risk.
* Targeted/cell therapies: Side effects vary; may include immune-related reactions.

## **How will treatment affect my usual routines, like work, hobbies, and time with family?**

Treatment can require hospital visits, recovery time, and may cause fatigue and physical limitations, especially after surgery or radiation. Many patients gradually return to normal activities, but some may need adjustments depending on treatment side effects and tumor location. Support from your healthcare team can help manage these challenges.

## **What are the chances my cancer will come back?**

Synovial sarcoma has a risk of recurrence, sometimes many years after treatment. The five-year survival rate is about 50–60%, and the five-year metastasis-free survival rate is 40–60%. Regular follow-up is essential to monitor for recurrence.

## 

## **Epidemiology**

In a cross-sectional study using data from Surveillance, Epidemiology, and End Results (SEER) 17 Registries, Patel et al determined that the incidence of primary synovial sarcoma in the United States between 2000 and 2020 was 0.15 per 100,000. The lower extremity was the most common primary tumor site, followed by the upper extremity, the abdomen and pelvis, the internal thorax, and the head and neck. Synovial sarcoma represents around 5-10% of all soft-tissue sarcomas.It is the third most common soft-tissue tumor in adolescents and young adults.

**DIFFERENTIAL DIAGNOSIS**.

1. MPNST- MPNST can be indistinguishable from monophasic synovial sarcoma, especially if the synovial sarcoma arises intra-neurally. Certain features that favor a diagnosis of MPNST are here:
   * The patient has a clinical history of neurofibromas.
   * The presence of several architectural patterns within the same lesion, along with the presence of focal atypia, favor MPNST. Likewise, the presence of goblet-type cells is seen only in glandular MPNST.
   * Focal CD-34 positivity exists (almost never seen in synovial sarcoma).
   * Negative CK-7 and CK-19 are present (most monophasic synovial sarcoma will stain for one or both).
   * SOX-10 stain has up to 63% sensitivity for diagnosing MPNST (positive for 7% synovial sarcoma) but has a very high specificity (93%) for diagnosing MPNST.
   * Lack of *SS18-SSX* fusions
2. Ewing Sarcoma/ Primitive Neuroectodermal Tumors (PNETs)
   * Can resemble poorly differentiated synovial sarcoma
   * Reticulin stain is positive in synovial sarcoma but negative in PNETs.
   * CD99 staining- Cytoplasmic pattern of staining in synovial sarcoma, vis-a-vis a strong membranous pattern in PNET
   * Expression of CK7 makes PNET less likely.
   * Caveolin-1 is positive in 95% of cases with EFT (membranous and cytoplasmic pattern). However, this is not specific to EFT.
   * TLE1 is rarely positive in EFT.
3. Epithelioid Sarcoma (ES)
   * 50% of ES may express CD34 which is never seen in synovial sarcoma
   * Diffuse expression of low and high molecular weight cytokeratin compared to focal presentation in synovial sarcoma.
4. Solitary Fibrous Tumor
   * Diffuse expression of CD34 and STAT6 in SFT is almost never seen in synovial sarcoma.
5. Dermatofibrosarcoma protuberans
   * Diffuse expression of CD34 and lack of keratin distinguish this from synovial sarcoma.
6. Gastrointestinal stromal tumor (GIST)
   * Important to know as synovial sarcoma is well characterized in the gastrointestinal tract. Hence, *KIT-negative* mesenchymal tumors could be synovial sarcoma.
   * DOG-1 is more commonly reported in GIST and is rarely reported in synovial sarcoma.
7. Infantile Fibrosarcoma
   * Occurs in the first two years of life
   * It does not express keratin
   * Characterized by t(12;15)(p13;q25), which gives rise to *ETV6-NTRK3* fusion.
8. Spindle cell Rhabdomyosarcoma
   * Express focal myogenin, which is not expressed in synovial sarcoma
9. Leiomyosarcoma - Can show focal dot keratin and rare EMA. Hence, it can be confused with synovial sarcoma.

## **Main Treatment Approaches for Synovial Sarcoma**

1. Surgery
   * Primary treatment for localized disease aiming for complete tumor removal with clear margins.
   * Limb-sparing surgery is preferred over amputation due to advances in surgical techniques.
2. Radiation Therapy
   * Used preoperatively to shrink tumors or postoperatively to kill residual cancer cells.
   * Side effects: fatigue, skin irritation, localized tissue fibrosis.
3. Chemotherapy
   * Often used before or after surgery, or for metastatic disease.
   * Common agents include:
     + Doxorubicin
     + Ifosfamide
     + Other drugs used in sarcoma protocols: Docetaxel, Gemcitabine, Paclitaxel, Trabectedin, Dacarbazine, Cyclophosphamide.
   * Side effects: nausea, vomiting, hair loss, fatigue, low blood counts, infection risk, kidney and heart toxicity (especially with doxorubicin).
4. Targeted and Cell Therapies
   * Afamitresgene autoleucel (Tecelra):
     + FDA-approved in August 2024 for advanced or metastatic synovial sarcoma expressing MAGE-A4 and in patients with HLA-A\*02.
     + This is a T-cell receptor (TCR) engineered cell therapy that enhances immune recognition of cancer cells.
     + Side effects include nausea, vomiting, fatigue, infections, and cytokine release syndrome (immune overreaction), which is mostly manageable.
     + Median response duration in trials was about 6 months.
5. Experimental Therapies
   * Research ongoing into targeting the SS18-SSX fusion protein pathway, such as degradation of WDR5, a protein interacting with SS18-SSX, showing promise in preclinical studies.
   * Clinical trials exploring novel immunotherapies, bromodomain inhibitors, and combination therapies.

## **STAGING**

## Tumor Size and Extent (T)

* T1: Tumor ≤5 cm in greatest dimension
* T2: Tumor >5 cm and ≤10 cm
* T3: Tumor >10 cm and ≤15 cm
* T4: Tumor >15 cm

*Note:* The distinction between superficial and deep tumors has been removed in the latest AJCC edition.

## 2. Lymph Node Involvement (N)

* N0: No regional lymph node metastasis
* N1: Regional lymph node metastasis present

Lymph node metastases are rare but considered significant.

## 3. Distant Metastasis (M)

* M0: No distant metastasis
* M1: Distant metastasis present (commonly lungs for synovial sarcoma)

## 4. Tumor Grade (G)

* G1: Low grade (well differentiated)
* G2: Intermediate grade
* G3: High grade (poorly differentiated or undifferentiated)

Tumor grade reflects how abnormal the cancer cells look and correlates with aggressiveness.

## **Genomic Features of Synovial Sarcoma**

* Pathognomonic Chromosomal Translocation:
  + Nearly 95% of synovial sarcomas harbor a specific chromosomal translocation t(X;18)(p11;q11).
  + This translocation fuses the SS18 (formerly SYT) gene on chromosome 18 with one of the SSX genes (SSX1, SSX2, or rarely SSX4) on the X chromosome, producing an oncogenic fusion protein SS18-SSX1/2.
  + This fusion protein is the primary driver of synovial sarcoma development and alters gene expression by disrupting chromatin remodeling complexes.
* Additional Somatic Mutations:
  + Synovial sarcomas generally have a low mutational burden beyond the SS18-SSX fusion.
  + However, next-generation sequencing studies have identified rare mutations in genes such as KRAS, CCND1, TP53, TERT, CDH1, CTNNB1, APC, HRAS, PTEN, RNF213, SEPT9, KDR, CSMD3, MLH1, and ERBB4.
  + Some mutations like KRAS and CCND1 are known oncogenic drivers in other cancers.
  + Additional mutations and chromosomal aberrations occur more frequently in adult-onset synovial sarcoma and metastatic lesions.
* Metastasis-Associated Mutations:
  + Comparative genomic analyses of primary and metastatic tumors have identified mutations unique to metastatic synovial sarcoma, such as missense mutations in ADAM17 that enhance cell migration and may contribute to metastasis.
  + Understanding these mutations may help unravel mechanisms of metastasis and identify therapeutic targets.
* Epigenetic Dysregulation:
  + The SS18-SSX fusion protein interferes with chromatin regulators like KDM2B, leading to aberrant gene activation and tumor growth.

**Doctor-patient conversation about synovial sarcoma,**

Doctor: Hello, I want to discuss your diagnosis of synovial sarcoma and what to expect moving forward.

Patient: Thank you, doctor. What exactly is synovial sarcoma?

Doctor: Synovial sarcoma is a rare type of soft tissue cancer that usually occurs near joints, often in the arms or legs. It arises from cells that have the potential to differentiate into various tissue types. It’s important to know that it’s a malignant tumor, but with proper treatment, many patients can do well.

Patient: What caused this cancer? Did I do something to cause it?

Doctor: The exact cause isn’t fully understood. However, almost all synovial sarcomas have a specific genetic change called the SS18-SSX fusion gene, which drives the cancer. This is a random event and not related to lifestyle or environment, so it’s not your fault.

Patient: Has the cancer spread?

Doctor: We’ve done imaging tests, and currently, it appears localized to the area near your joint. We will continue monitoring closely because synovial sarcoma can sometimes spread, most commonly to the lungs.

Patient: What treatment options do I have?

Doctor: The main treatment is surgery to remove the tumor completely. Depending on the tumor size and location, we may recommend radiation therapy before or after surgery to reduce the risk of recurrence. Chemotherapy may also be advised, especially if the tumor is large or if there’s concern about spread. Recently, a new cell therapy called afamitresgene autoleucel has been approved for advanced cases, which harnesses your immune system to fight the cancer.

Patient: What side effects should I expect from these treatments?

Doctor: Surgery may cause pain and require some recovery time, but our goal is to preserve as much function as possible. Radiation can cause fatigue and skin irritation. Chemotherapy side effects include nausea, hair loss, and increased infection risk. The new cell therapy can cause immune-related side effects, but these are usually manageable with close monitoring.

Patient: How will treatment affect my daily life, like work and family time?

Doctor: Treatment will require hospital visits and some downtime, especially after surgery and during chemotherapy. Fatigue is common, so you may need to adjust your routine temporarily. Many patients return to their usual activities gradually, and we have support services to help you and your family during this time.

Patient: What are the chances the cancer will come back?

Doctor: Synovial sarcoma can recur, sometimes years after treatment. The five-year survival rate is about 50–60%. Regular follow-up with imaging and exams is essential to catch any recurrence early when it’s more treatable.

Patient: Are there support groups or resources for patients like me?

Doctor: Yes, we have a dedicated sarcoma support group that meets regularly, and I can connect you with counselors and patient education resources. Being part of a support network can be very helpful.

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**Undifferentiated Pleomorphic Sarcoma**

**Definition and description**

Undifferentiated pleomorphic sarcoma (UPS) is a type of soft tissue sarcoma. It usually starts in the soft tissues of your arms or legs, or the back part of your belly (retroperitoneum). Rarely, UPS can affect your bones. It’s typically aggressive, so it can spread to other areas of your body — usually to your lungs or lymph nodes.

The original name for UPS was malignant fibrous histiocytoma. That’s because researchers thought this type of cancer formed in specialized immune cells called histiocytes. But later research suggested that it likely starts in mesenchymal cells that form connective tissue. The term “undifferentiated” refers to the fact that the cancer cells are very disorganized.

“Pleomorphic” means that the cells vary in size, shape or nuclei (the structure in a cell that contains chromosomes). In other words, UPS cells grow very haphazardly.

Overall, UPS is rare, affecting fewer than 5,000 people in the U.S. But it’s one of the three most common soft tissue sarcomas, along with liposarcoma and leiomyosarcoma.

**Symptoms and Causes**

Undifferentiated pleomorphic sarcoma symptoms might include:

* A growing lump
* A painless lump or mass that may or may not move when you touch it
* Numbness or tingling if a lump or mass is pushing on or arising from a nerve
* Swelling in an arm or leg

UPS doesn’t always cause noticeable symptoms. It’s most often painless, doesn’t have any skin changes over the top and doesn’t typically cause symptoms like fever, weight loss or general malaise.

**Undifferentiated pleomorphic sarcoma causes**

Experts aren’t sure what causes undifferentiated pleomorphic sarcoma. They know it happens when healthy cells develop changes in their DNA, but they don’t know what causes those changes.

**Risk factors**

risk factors for UPS include:

* Being male (white males have the highest risk)
* Being over the age of 50
* Certain diseases like neurofibromatosis or Paget’s disease of bone
* Certain genetic disorders like Li-Fraumeni syndrome
* Exposure to certain chemicals like arsenic or vinyl chloride
* History of radiation therapy to the affected area
* Occupational radiation exposure

Most people who develop UPS don’t have any known risk factors. A risk factor is something that increases your chances of getting a condition. Known

**Diagnosis and Tests**

Your healthcare provider will start by reviewing your health and biological family history. They’ll also ask questions about your symptoms, like when they started and whether they’ve changed over time. They’ll also do:

* **A physical exam**. They’ll check the size of the lump and feel its location and how hard it is.
* **Imaging tests**. These typically include X-rays, an ultrasound and/or an MRI.
* **Biopsy**. Your provider will take a small sample of tissue and send it to a pathologist for testing. This involves looking at the sample under a microscope.

**Management and Treatment**

Undifferentiated pleomorphic sarcoma treatment depends on the size of the tumor and whether the cancer has spread. The main treatment for early-stage UPS is typically surgery to remove the growth, most often combined with radiation therapy. But you might need additional cancer treatments, too.

**Surgery**

Surgery for undifferentiated pleomorphic sarcoma involves removing the tumor. The goal is to remove the entire sarcoma and a little bit of the healthy tissue around it (known as “the margin”). Your surgeon does this to improve the chances of removing all the cancer cells. If cancer cells are at the edge of the removed tumor, there’s a risk that some may be left in your body as well.

If UPS affects your arms or legs, your surgeon will try to remove the cancer and preserve as much function as possible. But in some cases, amputation may be necessary. Ask your oncologist what type of treatment they recommend for your situation.

**Additional cancer treatments**

Oncologists may also use additional treatments before or after surgery. These treatments rarely shrink the tumor, but they can help make the tumors safer to remove at surgery or treat any remaining cancer cells after surgery:

* Chemotherapy
* Immunotherapy
* Radiation therapy

Your treatment plan is unique to you. Ask your oncologist about your options. You’ll likely have a multidisciplinary team, including a surgeon, a radiation oncologist and a medical oncologist. Each specialist has a specific role, but they all work together to treat you. They can help you determine what’s best in your situation.

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

You should see a healthcare provider right away any time you notice a growing lump or mass — especially if it occurs with pain, swelling or limited range of motion.

If you already know you have UPS, tell your oncologist right away if you develop any new or worsening symptoms.

**Outlook / Prognosis**

Life expectancy varies depending on the size and stage of the sarcoma. The five-year survival rate for high-grade UPS is about 60%. That means that around 60% of people diagnosed with this condition are still alive five years later. The 10-year survival rate is 48%.

Survival rates are just estimates. They can’t tell you how long you’ll live or what kind of treatment will work for you. To learn more about UPS survival rates and how they affect you, talk to your oncology team.

**Is undifferentiated pleomorphic sarcoma curable?**

It’s possible to cure UPS, especially during the early stages. There still may be treatment options in later stages, which can prolong your quality of life. Like any type of cancer, early detection and treatment increase your chances for successful outcomes.

**DIFFERENTIAL DIAGNOSIS**

## Differential Diagnoses of Undifferentiated Pleomorphic Sarcoma

* Pleomorphic leiomyosarcoma
  + Positive for smooth muscle markers desmin and h-caldesmon.
  + Shows smooth muscle differentiation.
* Pleomorphic rhabdomyosarcoma
  + Expresses muscle markers desmin and myogenin.
  + Indicates skeletal muscle differentiation.
* Dedifferentiated liposarcoma
  + Characterized by amplification of MDM2 and CDK4 genes.
  + Shows areas of well-differentiated liposarcoma alongside undifferentiated sarcoma.
* Poorly differentiated carcinoma
  + Positive for epithelial markers such as MUC1 (EMA), TP63 (p63/p40), and keratins.
* Melanoma (including amelanotic melanoma)
  + Positive for S100, MLANA, and HMB-45 (PMEL).
* Pleomorphic liposarcoma
  + Presence of pleomorphic lipoblasts (immature fat cells) on histology.
* Malignant peripheral nerve sheath tumor (MPNST)
  + Often shows S-100 positivity, arranged in whorls or fascicles, may arise from neurofibromas.
* Myxofibrosarcoma
  + Characterized by myxoid stroma and pleomorphic cells, often with curvilinear blood vessels.
* Synovial sarcoma
  + May mimic UPS but usually shows specific translocation t(X;18) and epithelial markers.
* Atypical fibroxanthoma
  + Usually superficial skin tumor; histologically similar but more superficial and less aggressive.
* Lymphoma
  + Usually shows lymphoid markers (CD45, CD20, CD3).
* Dermatofibrosarcoma protuberans
  + Typically CD34 positive, with storiform pattern.
* Squamous cell carcinoma
  + Positive for keratins and p63.

EPIDEMIOLOGY

The 2020 World Health Organization classification of STSs incorporates UPS under malignant tumors of uncertain differentiation. According to the Surveillance, Epidemiology and End Results (SEER) program, UPS accounted for 17.1% out of 26,758 cases and was the second most common STS after leiomyosarcoma, regardless of the primary tumor site. Males showed considerably increased incidence rates than females, and white males were more commonly affected than black males. Incidence also linearly increased with advanced age, which was higher beyond the 6th decade of life

## **Main Treatment Approaches for UPS**

1. Surgery
   * The cornerstone of treatment is wide surgical excision with negative margins to reduce local recurrence risk.
   * Limb-sparing surgery is preferred when possible; amputation is rare but may be necessary in some cases.
2. Radiation Therapy
   * Used preoperatively, intraoperatively, or postoperatively, especially when margins are close or positive, or when tumors involve critical structures.
   * Helps reduce local recurrence but can cause fatigue, skin irritation, and long-term tissue fibrosis.
3. Chemotherapy
   * Not standard for all UPS patients but recommended for high-risk, high-grade, large tumors, or when radiation is contraindicated.
   * Common regimens include:
     + Anthracyclines (e.g., doxorubicin) plus ifosfamide (the “A + I” regimen), often first-line.
     + Docetaxel plus gemcitabine is also used, especially as neoadjuvant therapy.
   * Neoadjuvant chemotherapy may shrink tumors, facilitate less extensive surgery, and act as a radiosensitizer.

## Common Chemotherapy Drugs and Side Effects

| **Drug** | **Common Side Effects** | **Serious Risks / Notes** |
| --- | --- | --- |
| Doxorubicin | Nausea, vomiting, hair loss, fatigue | Cardiotoxicity (heart damage), myelosuppression |
| Ifosfamide | Nausea, vomiting, fatigue, hemorrhagic cystitis | Neurotoxicity, nephrotoxicity |
| Docetaxel | Fluid retention, neuropathy, fatigue | Hypersensitivity reactions |
| Gemcitabine | Flu-like symptoms, rash, nausea, fatigue | Myelosuppression, liver toxicity |

## Additional Treatment Considerations

* Immunotherapy and Targeted Therapy:
  + Currently under investigation; no established standard yet for UPS.
  + Molecular profiling may guide future personalized treatments.

**Alternative medicine**

No alternative treatments have been found helpful in treating undifferentiated pleomorphic sarcoma. But some complementary and alternative treatments may relieve the symptoms you experience due to cancer or cancer treatment.

Alternative treatments that may help relieve symptoms include:

* Acupuncture.
* Exercise.
* Massage.
* Meditation.
* Music therapy.
* Relaxation exercises.

## 

## **QUESTION AND ANSWER SET**

## **Do I have cancer?**

Yes, undifferentiated pleomorphic sarcoma is a type of high-grade soft tissue cancer. Diagnosis is confirmed by biopsy and pathology after ruling out other tumor types.

## **Are there other possible causes for my symptoms?**

Yes, symptoms like a painless lump or swelling can be caused by benign tumors, cysts, infections, or other non-cancerous conditions. Imaging and biopsy help distinguish UPS from these.

## **What kinds of tests do I need to confirm the diagnosis? Do these tests require any special preparation?**

* Physical exam to assess the lump’s size, depth, and relation to nearby structures.
* Imaging tests: MRI is preferred for detailed soft tissue evaluation; CT and PET scans may be used to check for metastases.
* Biopsy: A tissue sample is taken via needle or surgery for microscopic examination. Proper biopsy planning by a sarcoma specialist is crucial to avoid complicating future surgery.  
  No special preparation is usually needed except fasting or medication adjustments if sedation or anesthesia is required.

## **What stage is the sarcoma?**

Staging depends on tumor size, grade, lymph node involvement, and distant spread (usually lungs). Your doctor will explain your specific stage after imaging and pathology results.

## **What treatments are available for undifferentiated pleomorphic sarcoma, and which do you recommend?**

* Surgery with wide margins is the primary treatment to remove the tumor completely.
* Radiation therapy is often recommended before or after surgery to reduce recurrence risk.
* Chemotherapy is generally reserved for large, deep tumors or metastatic disease.  
  Treatment plans are individualized based on tumor size, location, and overall health.

## Can the sarcoma be removed?

In most cases, yes, if detected early and surgery is performed by an experienced orthopedic oncologist. Complete removal with clear margins is critical to reduce recurrence.

## **What types of side effects can I expect from treatment?**

* Surgery: pain, swelling, possible functional limitations depending on tumor location.
* Radiation: fatigue, skin changes, possible long-term tissue fibrosis.
* Chemotherapy: nausea, hair loss, fatigue, increased infection risk, and potential organ toxicities.

## **Are there any alternatives to the primary approach that you're suggesting?**

Alternatives depend on tumor specifics; sometimes, radiation alone or chemotherapy may be used if surgery is not feasible. Clinical trials may offer new options.

## **I have other health conditions. How can I best manage these conditions together?**

Your treatment team will coordinate care to manage other health issues alongside cancer treatment, adjusting therapies as needed to ensure safety.

## **Are there any dietary or activity restrictions that I need to follow?**

No strict universal restrictions, but maintaining good nutrition and avoiding strenuous activity during treatment is advisable. Your care team will provide personalized guidance.

## **What's my prognosis?**

Prognosis depends on tumor size, grade, stage, and treatment response. Early-stage UPS treated with surgery and radiation has better outcomes, but UPS can be aggressive with a risk of recurrence.

## **Should I get additional treatments such as radiation therapy either before or after an operation?**

Radiation therapy is commonly recommended either before surgery (to shrink the tumor) or after surgery (to kill remaining cancer cells), depending on your case.

## **Is the surgeon you're recommending experienced in this specific type of cancer operation?**

It is very important that your surgeon is an orthopedic oncologist or surgical oncologist with experience in sarcomas, as specialized expertise reduces recurrence risk and preserves function.

## **Genomic Alterations in Undifferentiated Pleomorphic Sarcoma**

* Frequent Mutated Genes:
  + TP53 mutations are the most common, found in approximately 66% of UPS cases, playing a critical role in tumor suppression loss.
  + ATRX mutations occur in about 34% of cases, involved in chromatin remodeling and telomere maintenance.
  + RB1 gene alterations are seen in roughly 28% of tumors, affecting cell cycle regulation.
  + Novel recurrent alterations include IL7R gene amplification (19%) and KMT2C mutations (16%), which may contribute to tumor progression and represent potential therapeutic targets.
* Pathways Involved:
  + Altered genes commonly affect key oncogenic pathways such as cell cycle regulation, PI3K/mTOR signaling, and RAS/MAPK pathways, driving proliferation, invasion, and survival.
  + High chromosomal instability and complex karyotypes with numerous structural and numerical chromosomal abnormalities are characteristic, including aneuploidy, trisomy, pentasomy, and hexasomy.
* Tumor Mutation Burden (TMB):
  + TMB tends to increase in recurrent UPS tumors, suggesting genomic evolution during progression and potential implications for immunotherapy.
* Additional Candidate Driver Genes:
  + Other genes implicated include H3F3A, ZFHX3, CSMD3, PRPRT, TRIO, CLTC, PDGFRB, ALK, PTCH1, RET, ERBB4, JAK3, GATA1, PIK3CG, RARA, and MYH9, many of which are involved in growth factor signaling, transcriptional regulation, and cell adhesion.

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**ANGIOSARCOMA**

**DEFINITION AND DESCRIPTION**

Angiosarcoma is a rare type of cancer that forms in the lining of the blood vessels and lymph vessels. The lymph vessels are part of the immune system. The lymph vessels collect bacteria, viruses and waste products from the body and dispose of them.

This type of cancer can occur any place in the body. But it most often occurs in the skin on the head and neck. Rarely, it may form in the skin on other parts of the body, such as the breast. Or it may form in deeper tissue, such as the liver and the heart. Angiosarcoma can occur in areas that were treated with radiation therapy in the past.

Treatment depends on where the cancer is located. Treatments may include surgery, radiation therapy and chemotherapy.

**Symptoms**

Angiosarcoma signs and symptoms may vary based on where the cancer occurs.

**Angiosarcoma that affects the skin**

Most often, angiosarcoma occurs in the skin on the head and neck. It often happens on the scalp. Symptoms of this form of angiosarcoma include:

* A raised area of skin that looks like a bruise
* A bruise-like lesion that grows larger over time
* A lesion that may bleed when scratched or bumped
* Swelling in the skin around the lesion

**Angiosarcoma that affects organs**

When angiosarcoma affects organs, such as the liver or the heart, it often causes pain. Other symptoms depend on the location of the angiosarcoma.

**When to see a doctor**

Make an appointment with your health care provider if you have any persistent symptoms that worry you.

**Causes**

It's not clear what causes most angiosarcomas. Researchers have identified factors that may increase the risk of the disease.

Angiosarcoma happens when cells in the lining of a blood vessel or lymph vessel develop changes in their DNA. A cell's DNA contains the instructions that tell the cell what to do. The changes, which doctors call mutations, tell the cells to multiply quickly. The changes cause the cells to keep living when healthy cells would die.

The result is a buildup of cancer cells that can grow beyond the blood vessel or lymph vessel. The cancer cells can invade and destroy healthy body tissue. In time, cancer cells may break away and spread to other areas of the body.

**Risk factors**

Factors that may increase the risk of angiosarcoma include:

* **Radiation therapy.** Treatment with radiation for cancer or other conditions may increase the risk of angiosarcoma. Angiosarcoma is a rare side effect of radiation therapy.
* **Swelling caused by lymph vessel damage.** Swelling caused by a backup of lymph fluid is called lymphedema. It happens when the lymphatic system gets blocked or damaged. Lymphedema can happen when lymph nodes are removed during surgery. This is often done during surgery to treat cancer. Lymphedema can also happen when there is an infection or other conditions.
* **Chemicals.** Liver angiosarcoma is linked to exposure to several chemicals. Examples of these chemicals include vinyl chloride and arsenic.
* **Genetic syndromes.** Certain gene changes that people can be born with can raise the risk of having angiosarcoma. Examples include the gene changes that cause neurofibromatosis, Maffucci syndrome, or Klippel-Trenaunay syndrome, and the *BRCA1* and *BRCA2* genes.

**Diagnosis**

Tests and procedures used in angiosarcoma diagnosis include:

* **Physical exam.** Your health care provider will thoroughly examine you to understand your condition.
* **Removing a sample of tissue for testing.** Your provider may remove a sample of suspicious tissue for laboratory testing. This procedure is called a biopsy. Tests in the lab can detect cancer cells. Special tests can give your provider more details about the cancer cells.
* **Imaging tests.** Imaging tests can give your provider an idea of the extent of the cancer. Tests may include MRI, CT and positron emission tomography (PET). Which tests you undergo will depend on your situation.

**Treatment**

Which angiosarcoma treatment is best for you depends on your situation. Your health care team considers the cancer's location, its size and whether it has spread to other areas of the body.

Treatment options may include:

* **Surgery.** The goal of surgery is to remove all of the angiosarcoma. Your surgeon will remove the cancer and some of the healthy tissue that surrounds it. Sometimes surgery isn't an option. This might happen if the cancer is very large or has spread to other areas of the body.
* **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 to kill any cancer cells that remain. Radiation therapy may also be an option if you can't have surgery.
* **Chemotherapy.** Chemotherapy is a treatment that uses drugs or chemicals to kill cancer cells. Chemotherapy may be an option if the angiosarcoma has spread to other areas of the body. Sometimes chemotherapy may be combined with radiation therapy if you can't undergo surgery.
* **Targeted drug therapy.** Targeted drug treatments attack specific chemicals present within the cancer cells. By blocking these chemicals, targeted drug treatments can cause cancer cells to die. For angiosarcoma treatment, targeted drugs might be an option if the cancer is advanced.
* **Immunotherapy.** Immunotherapy uses the immune system to fight cancer. Your body's immune system might not attack your cancer because the cancer cells make proteins that help them hide from the immune system's cells. Immunotherapy works by interfering with that process. For angiosarcoma, immunotherapy might be a treatment option for advanced cancer.

**Outlook / Prognosis**

Angiosarcomas can spread fast because they start in your blood vessels. Once it’s spread, angiosarcoma is very difficult to treat. Even in those cases where it goes away after treatment, it often comes back (recurs).

Healthcare providers are identifying more effective ways of treating angiosarcoma, but the survival rate is still low. About 35% of people diagnosed with angiosarcoma are alive five years after diagnosis.

**Prevention**

Not all causes of angiosarcoma are preventable. For example, you can’t help inheriting a genetic condition or needing radiation therapy for cancer. But there are things you can do to reduce some risks of developing angiosarcoma, like limiting your exposure to certain toxic chemicals.

**Living With**

Angiosarcoma is a fast-moving cancer. You can take care of yourself by slowing down. Try to give yourself time to understand what’s happening to your body. Talk to your healthcare provider about steps you can take to support your treatment. Here are some suggested steps that may help:

* **Try to ease your stress**. If you’re feeling extra stressed after learning of your diagnosis, you’re not alone. Cancer is stressful. You may find activities like meditation, relaxation exercises or deep breathing help.
* **Allow yourself to rest**. You may feel very tired or “wiped out” after your cancer treatments. Try to get as much rest as you can.
* **Try to eat healthy foods regularly**. Your treatments might affect your appetite. Try to eat nutritious foods (without skipping meals). Talk to a dietitian if you’re having trouble eating.
* **Connect with others**. Cancer can be lonely, especially when you’re dealing with a rare cancer like angiosarcoma. Ask your provider to connect you to support groups where you can share your feelings with people who understand what you’re going through.

**DIFFERENTIAL DIAGNOSIS**

AS is one of the over 70 different subtypes of STS. It is also included in the broad category of the vascular tumors that make the bulk of differential diagnosis for AS.

* Reactive and benign vascular tumors
  + Capillary haemangiomas
  + Juvenile haemangioma (strawberry naevus)
  + Cherry angioma (Campbell de Morgan spot)
  + Pyogenic granuloma
  + Cavernous haemangiomas
  + Epithelioid haemangioma
  + Vascular ectasis (naevus flammus, spider naevus)
  + Angiomatosis
  + Postradiation atypical vascular lesion
* Intermediate grade vascular tumors
  + Kaposi’s sarcoma
  + Epithelioid haemangioendothelioma
* Malignant vascular tumors
  + Angiosarcoma
* Tumors of perivascular cells
  + Haemangiopericytoma (solitary fibrous tumor)

**Angiosarcoma Epidemiology**

* Incidence:
  + Angiosarcoma is a *rare* and aggressive soft tissue sarcoma.
  + In Japan, the age-adjusted incidence is approximately 0.18 per 100,000 person-years.
  + In Western countries, incidence rates are somewhat higher: about 0.26 per 100,000 in France and 0.30 per 100,000 in the United States.
  + Overall, angiosarcoma accounts for roughly 8.4% of all soft tissue sarcomas in Japan.
  + The incidence has shown a slight increase over recent decades, particularly among older adults (65 years and above).
* Demographics:
  + Angiosarcoma tends to occur more frequently in older adults, with a higher incidence in people aged 65 and older.
  + In Japan, a male predominance (~59%) was reported, whereas some Western studies show a slight female predominance, partly due to breast-related angiosarcomas.
  + The most common tumor location is the head and neck region (about 51% in Japan), followed by soft tissue, visceral organs, and breast.
* Trends:
  + The number of angiosarcoma cases is gradually increasing, partly due to secondary angiosarcomas arising after breast cancer treatment (radiation-induced).
  + Age-adjusted incidence rates have increased from about 1 to 3 per 100,000 population over several decades in some registries.
* Survival and Prognosis:
  + Angiosarcoma carries a poor prognosis compared to other sarcomas.
  + Reported 3-year overall survival rates are around 25–34%, and 5-year survival rates approximately 26–27%.
  + Prognosis varies by tumor location, with visceral angiosarcomas having worse outcomes than cutaneous or breast angiosarcomas.

**STAGING**

* T1: Tumor ≤ 5 cm
* T2: Tumor > 5 cm and ≤ 10 cm
* T3: Tumor > 10 cm and ≤ 15 cm
* T4: Tumor > 15 cm  
  (For cutaneous angiosarcoma, T2 tumors (>5 cm) are associated with poorer prognosis and higher risk of positive margins.) |  
  | N (Lymph nodes) |
* N0: No regional lymph node metastasis
* N1: Regional lymph node metastasis present (rare but significant) |  
  | M (Metastasis) |
* M0: No distant metastasis
* M1: Distant metastasis present (lungs are the most common site) |  
  | G (Grade) | Based on pathology scoring:
* Differentiation (1–3),
* Mitotic count (1–3),
* Tumor necrosis (0–2)  
  Sum determines grade:
* G1 (low grade), G2 (intermediate), G3 (high grade) |

## **Common Genetic Alterations**

* TP53 mutations (~29–31%)
  + Tumor suppressor gene frequently mutated across angiosarcomas, especially in head and neck AS (50%).
* MYC amplification (~23%)
  + Highly enriched in breast AS (up to 63%) and extremity AS. MYC amplification is associated with cell cycle dysregulation.
* POT1 mutations (~16%)
  + Particularly prevalent in head and neck AS (40.5%), involved in telomere maintenance and genomic stability.
* ARID1A mutations (~17%)
  + Chromatin remodeling gene mutated in a significant subset, potentially linked to epigenetic dysregulation.
* ATRX mutations (~13%)
  + Involved in chromatin remodeling and telomere maintenance.
* HRAS and PIK3CA mutations (~16% in breast AS)
  + Affect RAS/MAPK and PI3K/AKT signaling pathways, respectively, contributing to oncogenic signaling.
* Other recurrently altered genes include KDR (VEGFR2), FLT4, PTPRB, RAS family genes, CRKL, ATM, and DNA damage repair (DDR) pathway genes.

## **Tumor Mutation Burden (TMB) and Immunotherapy Markers**

* High TMB and PD-L1 expression are more common in head and neck angiosarcomas (TMB-High in ~63%, PD-L1+ in 33%), indicating potential responsiveness to immunotherapy.
* Microsatellite instability (MSI) is rare (~0.7%).
* A subset (~13%) of angiosarcomas across sites shows a microenvironment enriched with immune cells, potentially predictive of immunotherapy benefit.

## 

## **QUESTION AND ANSWER SET**

## **How advanced is my angiosarcoma?**

The stage of your angiosarcoma depends on tumor size, location, grade, and whether it has spread. Your healthcare team uses imaging tests (MRI, CT, PET) and biopsy results to determine this. Angiosarcoma can grow quickly and often presents at an advanced stage, but exact staging requires your doctor’s assessment.

## **Has my angiosarcoma spread to other parts of my body?**

Angiosarcoma commonly spreads to the lungs and sometimes to lymph nodes or other organs. Imaging scans help detect metastases. If spread (metastasis) is present, treatment options and prognosis may be affected.

## **What treatments do you recommend?**

Treatment depends on your cancer’s extent and health status. Options include:

* Surgery to remove the tumor, if feasible.
* Radiation therapy before or after surgery to kill remaining cancer cells or if surgery isn’t possible.
* Chemotherapy for advanced or metastatic disease.
* Targeted therapies that attack specific molecules in cancer cells.
* Immunotherapy, especially immune checkpoint inhibitors, has shown promise in advanced angiosarcoma, particularly in scalp/face tumors or those with high mutation burden.

## **What are the benefits and risks of each treatment option?**

* Surgery: Potentially curative if complete removal is possible; risks include pain, infection, and functional loss depending on tumor location.
* Radiation: Can improve local control; side effects include fatigue and skin irritation.
* Chemotherapy: May control spread but can cause nausea, hair loss, fatigue, and immune suppression.
* Targeted therapy: Often better tolerated but may have specific side effects depending on the drug.
* Immunotherapy: Can produce durable responses; side effects include immune-related inflammation but are often manageable.

## **I have other health problems. How can I best manage them together?**

Your healthcare team will coordinate care to safely manage your other conditions alongside cancer treatment, adjusting therapies as needed to minimize risks and maintain overall health.

## **Will I be able to work and do my usual activities during angiosarcoma treatment?**

Treatment can affect energy levels and physical function. Many patients experience fatigue and need time off work or reduced activity, especially during chemotherapy or radiation. Your team can help plan supportive care to maintain quality of life.

## **Should I seek a second opinion?**

Yes, getting a second opinion, especially from a sarcoma or cancer center specialist, is advisable to confirm diagnosis and explore all treatment options.

## **Should I see a doctor who treats cancer?**

Absolutely. Angiosarcoma is best managed by a multidisciplinary team including oncologists, surgeons, radiation specialists, and supportive care providers experienced in sarcomas.

## How quickly do I need to make a decision about treatment? Can I take some time to consider my options?

While angiosarcoma can progress rapidly, you should discuss with your doctor the urgency of starting treatment. Usually, there is time to consider options, ask questions, and seek second opinions without compromising outcomes

**treatment of angiosarcoma:**

* Paclitaxel
* Anthracycline-based regimens
* Gemcitabine-based regimens

Anthracycline-based regimens include the following:

* Doxorubicin
* Epirubicin
* Liposomal doxorubicin
* AD (doxorubicin, dacarbazine)
* AIM (doxorubicin, ifosfamide, mesna)
* Ifosfamide, epirubicin, mesna

Gemcitabine-based regimens include the following:

* Gemcitabine and docetaxel
* Gemcitabine and vinorelbine
* Gemcitabine and dacarbazine

Neoadjuvant chemotherapy can be considered in patients with large localized angiosarcomas, where achieving negative margins may be a challenge. However, response to preoperative chemotherapy is only 40-50% with the most active regimens, and toxicity is significant. European guidelines list neoadjuvant chemotherapy as an option in selected patients with high-risk local or locoregional disease.

Angiosarcoma is highly sensitive to taxanes, and paclitaxel has proved well tolerated and active even in pretreated patients with locally advanced or metastatic angiosarcoma. Paclitaxel is used as single-agent therapy and is administered weekly

Radiotherapy can be delivered intraoperatively, by brachytherapy, or by external beam radiotherapy (EBRT). The brachytherapy technique results in rates of tumor control similar to those obtained with EBRT, with a similar rate of wound complications. Moreover, it presents the advantage of requiring only 5 days, rather than the 5-6 weeks needed for EBRT, and reduces radiation scatter. Brachytherapy is often the technique of choice in angiosarcomas near joints or gonads.

The use of irradiation in conjunction with surgery continues to evolve and results in 80% of local control and excellent functional and cosmetic outcome.However, consider that 50% of angiosarcomas have distant metastases, and irradiation does not improve survival. Better definition of the extent of the disease with the use of MRI helps to further delineate the radiotherapy fields and decrease long-term morbidity. Intraoperative radiation, brachytherapy, or more EBRT can complement preoperative EBRT.

The disadvantage of preoperative radiation is that a higher wound complication rate may delay surgery (1 wk of healing per 10 Gy of radiation delivered). The advantages of preoperative radiation are as follows:

* Optimization for surgery
* Smaller volume of external beam fields
* Less hypoxic tissue
* Potential to reduce the chance of intraoperative implantation
* Potential improvement in local control in advanced tumors

### Bone angiosarcoma

In bone angiosarcoma, specialists use combinations of radiation therapy and chemotherapy for adjuvant treatment, but significant data about their effectiveness are lacking. Evidence of tumor multicentricity must be sought before making any decision regarding therapy. Patients have presented with lesions affecting as many as 45 different bones. In such cases, consider neoadjuvant chemotherapy.

A chemotherapeutic regimen common for sarcomatous tumors can be administered (ifosfamide and doxorubicin used together or sequentially). If clinical or radiographic improvement is not observed, consider a second regimen with cyclophosphamide, etoposide, and cisplatin. Gemcitabine may be effective as second-line or third-line therapy.

### Cutaneous angiosarcoma

The best outcomes are reported with surgery followed by radiotherapy. Postoperative radiotherapy is warranted in cases with unsatisfactory margins, large tumor size, deep extension, and multicentricity. Radical radiation therapy in the form of high-field electron beam therapy shows promise in prolonging survival of patients with localized lesions.

Paclitaxel as a single agent has shown substantial activity against cutaneous angiosarcoma, even in patients previously treated with chemotherapy or radiation therapy. Solid evidence supports first-line use of paclitaxel in advanced cutaneous angiosarcoma. Immune checkpoint inhibitor therapy, such as with ipilimumab plus nivolumab, or pembrolizumab, has shown benefit in cutaneous angiosarcoma.Other options for second-line treatment include pazopanib, eribulin, and trabectedin.

## Surgical Care

Surgical treatment of angiosarcoma of the soft tissue, retroperitoneum, and abdomen is as follows:

* Target obtaining wide surgical margins, with at least 2 cm of unaffected tissue surrounding the tumor. The resection should include skin when applicable and the soft tissue around the angiosarcoma. Resect biopsy sites, including the biopsy tract, en bloc with the specimen.
* Resection of large lesions can be extremely difficult and sometimes requires amputation for local control; however, local control does not prevent distant relapse.
* Free surgical margins sometimes have anatomic constraints, especially in retroperitoneal tumors.

Surgical treatment of angiosarcoma of bone is as follows:

* Surgical resection and radiation therapy are the standard treatment for localized disease.
* Low-grade lesions lead to similar benefits with either technique.
* Treat high-grade lesions as malignant bone neoplasms, with a combination of radical en bloc excision followed by radiotherapy and/or chemotherapy.
* The number of lesions in a limb may render limb salvage impossible, and amputation may be indicated.

Surgical treatment of cutaneous angiosarcoma is as follows:

* Surgical treatment is contraindicated in tumors extending into vital structures, in those of massive size, or in those with multicentricity.
* The lesion may be solitary or multicentric and frequently extends laterally throughout the dermis, making gross assessment of surgical margins difficult and necessitating multiple biopsies of the surrounding tissues.
* In the primary treatment of angiosarcomas of the scalp, recognizing the horizontal and vertical extensions of the tumor is essential, which can be discerned only by microscopic examination of all the margins of the resected specimen. The primary excision of the scalp should be full-thickness, including the pericranium and, if indicated, the outer table of the cranial vault; the margins should be wide (at least 5 cm) on all sides.

## **Complications**

Complications from radiotherapy include the following:

* Wound complications
* Fractures

Complications from chemotherapy include the following:

* Fever
* Dose-dependent myelosuppression
* Nausea and vomiting unresponsive to antiemetics
* Moderate-to-severe fatigue
* Alopecia or hemialopecia in intra-arterial chemotherapy

Complications from surgery are as follows:

* Anesthetic complications
* Blood loss
* Infection, sepsis
* Wound complications
* Iatrogenic neurovascular injury
* Deep vein thrombosis, pulmonary embolism
* Limited limb function

**Doctor-patient conversation about angiosarcoma**,

Doctor:  
“Thank you for coming in today. I want to discuss the results of your biopsy. The diagnosis is angiosarcoma, which is a rare and aggressive cancer that starts in the cells lining blood vessels or lymph vessels. It can grow quickly and sometimes spread to other parts of the body.”

Patient:  
“That sounds serious. What does this mean for me? What are my treatment options?”

Doctor:  
“I understand this is difficult news. Angiosarcoma can behave differently depending on where it started, its size, and whether it has spread. Treatment usually involves surgery to remove the tumor if possible, often combined with radiation therapy to reduce the chance of it coming back. Chemotherapy, targeted therapies, or immunotherapy may also be options, especially if the cancer has spread or can’t be fully removed.”

Patient:  
“Will the surgery be extensive? What about side effects?”

Doctor:  
“The goal is to remove all of the cancer with clear margins, which sometimes means a larger operation depending on the tumor’s location. Side effects depend on the treatment type and area involved, but we will work closely with you to manage them and support your recovery.”

Patient:  
“Is the prognosis good? What are the chances of the cancer coming back?”

Doctor:  
“Angiosarcoma is known to be aggressive, and unfortunately, it has a higher risk of recurrence and spread compared to many other cancers. Prognosis depends on factors like tumor size, location, and how completely we can remove it. Smaller tumors and complete removal improve outcomes. We will monitor you closely after treatment to catch any recurrence early.”

Patient:  
“Should I see a specialist?”

Doctor:  
“Absolutely. Because angiosarcoma is rare and complex, I will refer you to a sarcoma specialist team experienced in managing this disease. They will help tailor the best treatment plan for you.”

Patient:  
“What can I do to prepare for treatment?”

Doctor:  
“Try to stay as healthy as possible, eat well, and keep a list of any questions or concerns. It’s also helpful to have a support person with you during appointments. We can provide you with educational materials and connect you with support groups for people with sarcomas.”

Patient:  
“Thank you for explaining everything clearly. It helps to know what to expect.”

Doctor:  
“You’re welcome. We’re here to support you every step of the way. Please don’t hesitate to reach out with any questions before your next visit.”

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**KAPOSI SARCOMA**

**DEFINITION AND DESCRIPTION**

Kaposi sarcoma creates patches of abnormal tissue that may appear in various places throughout your body, including your arms and legs.

Kaposi sarcoma (KS) is a type of soft tissue sarcoma. It causes lesions that can form on your skin or mucus membranes that line the inside of your mouth, nose and anus. These tumors may also develop in the lining of internal organs like your liver, belly and lungs.

You can get KS if you carry human herpesvirus 8 (HHV-8) and have a weakened immune system. KS is rare. Fewer than 5,000 people living in the United States have it.

**Types of Kaposi sarcoma**

There are four types of Kaposi sarcoma. From most to least common, they are:

* **Epidemic KS.** Related to AIDS/HIV, this is the most common type of Kaposi sarcoma in the U.S.
* **Classic KS.** This type of KS mostly affects males over 60 who are of Mediterranean, Southwest Asian, Eastern European or Ashkenazi Jewish descent. Lesions might also spread to internal organs.
* **Endemic KS.** This type of KS affects people living near the African equator. It is similar to classic KS, but the age of diagnosis is usually much younger (under age 40).
* **Acquired KS.** You can get this type if you carry HHV-8 and take immunosuppressants after an organ or bone marrow transplant.

**Symptoms and Causes**

Kaposi sarcoma symptoms can vary depending on the location of the lesions. You might develop:

Kaposi sarcoma signs and symptoms include:

* A growth on the skin that may be raised or flat.
* A growth on the skin that looks red, purple or brown in color.

The growths, called lesions, most often happen on the face, arms or legs. They usually don't cause discomfort.

If Kaposi sarcoma isn't treated, the lesions can get bigger. They may cause:

* Swelling in the lower legs caused by blood flow problems.
* Enlarged lymph nodes.
* Skin that appears red or purple in color and may be painful and itchy.

Kaposi sarcoma also can affect areas you can't see. It can grow in the digestive tract or lungs. When Kaposi sarcoma happens in the digestive tract, symptoms may include:

* Diarrhea.
* Nausea.
* Stomach pain.
* Vomiting.
* Weight loss.

**Kaposi sarcoma causes**

Kaposi sarcoma happens when HHV-8 infects the cells that line your blood and lymphatic vessels. HHV-8 is a rare disease that turns healthy cells into cancerous cells. Certain factors increase the risk of HHV-8 becoming Kaposi sarcoma.

**Risk factors**

Risk factors for Kaposi sarcoma include:

* **Age.** Kaposi sarcoma mostly affects those between ages 40 and 70.
* **Ethnicity.** You have a higher risk for KS if you’re of Mediterranean, Southwest Asian, Eastern European or Ashkenazi Jewish descent.
* **Immune deficiency.** You’re more likely to develop KS if you have a weakened immune system. This can happen from taking immunosuppressants or having conditions like HIV/AIDS.
* **Location.** You have a higher risk for endemic KS if you live near the equator in Africa.
* **Sex.** Males are more likely to develop Kaposi sarcoma.
* **Sexual activity.** Having unprotected sex can increase your risk of contracting HHV-8 and HIV. These viruses typically spread through bodily fluids.

**Complications of Kaposi sarcoma**

Kaposi sarcoma can lead to complications, which may include:

* Anemia
* Breathing issues
* Pain
* Second cancer
* Skin abnormalities
* Skin swelling and disfigurement

**Diagnosis and Tests**

### **Taking a piece of skin for testing**

A healthcare professional may recommend removing a small piece of a skin lesion for testing. This procedure is called a skin biopsy. The sample is sent to a lab for testing. Lab tests can look for signs of cancer.

A skin biopsy can confirm Kaposi sarcoma.

### **Testing for Kaposi sarcoma inside the body**

Other tests might be needed to look for Kaposi sarcoma in the lungs or the digestive tract.

Tests to find Kaposi sarcoma in the digestive tract might include:

* **Fecal occult blood test.** This test detects hidden blood in stool. If it shows hidden blood, other tests might be needed to find the source. Other tests include an endoscopy or colonoscopy. These tests are used to see if Kaposi sarcoma is causing the bleeding.
* **Endoscopy.** In this test, a thin tube, called an endoscope, is passed through the mouth. It allows a healthcare professional to look at the esophagus, stomach and first part of the small intestine.
* **Colonoscopy.** In this test, a thin tube called a colonoscope goes through the rectum and into the colon. It allows a health professional to look at the walls of these organs.
* **CT scan.** This imaging test uses X-rays to make detailed images of the inside of the body. A CT of the abdomen and pelvis can show the digestive tract.

**Tests that are used**

To get an accurate diagnosis, your healthcare provider will need to run tests, which may include:

* **Biopsy.** Your provider takes a small tissue sample and sends it to a pathologist for testing.
* **Bronchoscopy.** This test helps your provider look for KS in your windpipe and the airways that lead to your lungs.
* **Chest X-ray.** They’ll take images of your lungs to look for KS lesions. You may also need a CT scan.
* **Endoscopy.** This test helps your healthcare provider look inside your stomach or intestines for KS lesions. Depending on your situation, you might need an upper endoscopy, a colonoscopy or both.
* **Immunohistochemistry.** This lab test looks for a specific protein called LANA-1. It’s associated with HHV-8. It helps your provider tell the difference between KS and similar lesions.

**Management and Treatment**

It depends on your situation. Your healthcare team will create a personalized plan unique to you. Treatments may include:

* Antiretroviral therapy
* Chemotherapy
* Cryotherapy
* Radiation therapy
* Surgery
* Targeted therapy

The treatment that’s right for you depends on a few different factors, like the type of KS you have, the number and location of lesions, and your overall health. Your oncologist can tell you what to plan for in your case.

There's no cure for Kaposi sarcoma. But there are many treatment options that can help control it. Some people may not need treatment right away. Instead, the condition might be monitored to make sure it's not getting worse. Treatment depends on:

* The type of Kaposi sarcoma.
* The number of lesions and where they are.
* The effects of the lesions, such as causing pain or getting in the way of eating or breathing.
* Your overall health.

### **Treatment for AIDS-related Kaposi sarcoma**

Thanks to better antiviral medicines to treat AIDS and ways to prevent it, Kaposi sarcoma has become less common and less severe in people with AIDS. Taking antiviral medicines can lower the amount of the virus that causes HIV/AIDS and make the immune system stronger. This might be the only treatment needed for Kaposi sarcoma.

### **Treatment for transplant-related Kaposi sarcoma**

Some people with transplant-related Kaposi sarcoma may be able to stop taking the medicines that are controlling the immune system or switch to another medicine.

### **Treatment for small skin lesions**

Treatments for small skin lesions might include:

* Minor surgery, also called excision.
* Freezing treatment, called cryotherapy.
* Radiation therapy.
* An injection of the chemotherapy medicine vinblastine into lesions.
* Applying a medicine cream or gel to the skin.

Lesions treated in any of these ways are likely to return within a couple of years. When this happens, treatment often can be repeated.

### **Treatment if there are many skin lesions**

If Kaposi sarcoma causes many skin lesions, other treatments might be needed, such as:

* **Radiation therapy.** Radiation therapy uses powerful energy beams to kill cancer cells. This is a treatment option if there are many skin lesions, but not enough to need chemotherapy.
* **Chemotherapy.** Chemotherapy uses strong medicines to kill cancer cells. Chemotherapy might be an option when Kaposi sarcoma affects multiple parts of the body. For Kaposi sarcoma that's getting worse quickly, chemotherapy might help.

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

Kaposi sarcoma can come back (recur) after treatment. So, you’ll have regular follow-ups so your healthcare provider can monitor your health and check for signs of new cancer.

If you’re living with HIV/AIDS or have had an organ transplant, your regular check-ups will include screenings for recurring KS.

**Outlook / Prognosis**

Your outlook depends on many factors. But like most cancers, early detection and treatment give you the best chance for long-term survival.

The overall five-year survival rate for Kaposi sarcoma is 75%. That means that 75% of people who have KS are still alive five years after their diagnosis.

Keep in mind that cancer survival rates are only estimates. They can’t predict how long you’ll live or how well you’ll respond to treatment. To learn more about survival rates and what they mean for you, talk to your healthcare provider.

**How can I take care of myself?**

If you have Kaposi sarcoma, maintaining a healthy immune system is the best thing you can do to take care of yourself. You can support your immune system by:

* Eating plenty of nutritious foods, like fresh fruits and veggies
* Getting enough sleep
* Limiting beverages that contain alcohol
* Managing stress
* Quitting smoking
* Staying up to date on vaccines
* Washing your hands often

**Prevention**

According to the American Cancer Society, taking steps to reduce your HIV risk may help prevent Kaposi sarcoma.

If you have HIV, highly active antiretroviral therapy can reduce your risk of developing Kaposi sarcoma and AIDS.

**Common Questions**

**I’m an organ transplant recipient. How can I reduce my risk of Kaposi sarcoma?**

Talk to your healthcare provider if you have HHV-8. There are immunosuppressant medications that protect your transplanted organ without increasing your risk of Kaposi sarcoma.

**Is Kaposi sarcoma an autoimmune disease?**

Kaposi sarcoma isn’t an autoimmune disease. It’s a type of cancer that usually affects people with weakened immune systems.

In other words, it happens when your immune system is already weak, not when your body attacks its own tissues.

## **What's likely causing my symptoms?**

Kaposi sarcoma is caused by infection with human herpesvirus 8 (HHV-8), also called Kaposi sarcoma-associated herpesvirus (KSHV). The virus infects the cells lining blood and lymph vessels, leading to tumor formation. Symptoms such as purple or red skin lesions, swelling, or organ symptoms arise from these tumors growing in skin, lymph nodes, or internal organs.

## **Other than the most likely cause, what are other possible causes for my symptoms?**

Other conditions that can look like KS include:

* Benign vascular lesions like angiomas or pyogenic granulomas
* Infectious causes such as bacillary angiomatosis
* Other cancers like melanoma or lymphoma
* Skin conditions like dermatophytosis or histiocytoma  
  A biopsy is needed to confirm the diagnosis.

## **What tests do I need?**

* Physical exam to check skin and mucosal lesions.
* Biopsy of a lesion to confirm KS by microscopic examination and detection of HHV-8 proteins.
* Imaging (CT scans) of chest, abdomen, and pelvis to check for internal involvement, especially in people with HIV or immunosuppression.
* Endoscopy or bronchoscopy if symptoms suggest lung or gastrointestinal involvement.

## **Does my condition have a cure?**

KS can often be controlled, especially with treatment of underlying immune suppression (e.g., antiretroviral therapy for HIV). Localized skin lesions may be treated successfully. However, widespread or visceral KS is generally not curable but can be managed to improve symptoms and quality of life.

## **What's the best course of action?**

* For people with HIV, starting or optimizing antiretroviral therapy (ART) is critical.
* Localized lesions may be treated with cryotherapy, radiation, or excision.
* More extensive disease may require chemotherapy or immunotherapy.
* Treatment plans are individualized based on lesion extent, symptoms, and immune status.

## **I have these other health conditions. How can I best manage them together?**

Managing KS alongside other health problems requires coordinated care. Optimizing immune function, controlling infections, and addressing symptoms holistically are important. Your healthcare team will tailor treatment to your overall health.

## **Should I see a specialist?**

Yes, seeing a dermatologist, oncologist, or infectious disease specialist experienced with KS and HIV-related cancers is recommended for accurate diagnosis and treatment planning.

## **What would happen if I choose not to have treatment?**

Without treatment, KS lesions can grow, merge, and spread to internal organs causing complications like swelling, bleeding, pain, breathing difficulties, and digestive problems. The disease may progress rapidly, especially in immunocompromised individuals

**DIFFERENTIAL DIAGNOSIS**

Histologically, spindle cell vascular lesions in the skin include a differential diagnosis of:

* Interstitial granuloma annulare
* Spindle cell hemangioma
* Acquired tufted angioma
* Kaposiform hemangioendothelioma
* Cutaneous angiosarcoma
* Fibrosarcomatous dermatofibrosarcoma protuberans
* Aneurysmal dermatofibroma
* Acroangiodermatitis
* Spindle cell melanoma
* High-grade sarcomas

The differential diagnosis of Kaposi sarcoma on mucocutaneous surfaces includes:

* Nevi
* Pyogenic granuloma
* Bacillary angiomatosis
* Hemangioma
* Angiosarcoma
* Melanoma

**EPIDEMIOLOGY**

Classic Kaposi sarcoma has a male: female ratio 17:1 and occurs primarily in patients over 50 years old of Eastern European and Mediterranean descent. These patients are at greater risk for secondary malignancies. The prevalence mirrors the distribution of HHV-8 throughout the world. Within the United States, incidence has been stable around 1:100,000 since 1997.

Endemic Kaposi sarcoma has the unusual predilection for the pediatric population and mirrors HHV-8 seropositivity. The rates of seropositivity in pediatric patients vary extensively throughout Africa, from a low of 2% in Eritrea to almost 100% in the Central African Republic.Following the HIV epidemic in Africa, the ratio of men to women with Kaposi sarcoma has fallen from 7:1 to 2:1.Endemic Kaposi sarcoma is now the most common cancer in men and the second most common cancer in women with Uganda and Zimbabwe.

HHV-8 seropositivity worldwide varies, with a high of 40% in Saharan Africa to 2% to 4% in Northern Europe, Southeast Asia, and Caribbean countries. Approximately 10% of Mediterranean countries and 5-20% of United States patients are seropositive for HHV-8. This unique predilection for sub-Saharan African, the Mediterranean, and South America is unique to HHV-8 amongst human herpesviruses.

AIDS-related Kaposi sarcoma is the second most common tumor in HIV patients with CD4 counts less than 200 cells/mm3 and is an AIDs-defining illness.Up to 30% of HIV patients not taking high-activity antiretroviral therapy (HAART) will develop Kaposi sarcoma. HIV positive male homosexuals have a 5- to 10-fold increased risk of Kaposi sarcoma.

Iatrogenic Kaposi sarcoma has a male: female ratio of 3:1. Over 5% of transplant patients who develop a de novo malignancy will develop Kaposi sarcoma, a 400- to 500-fold increased risk over the general population. Patients with bone marrow or peripheral blood stem cell transplant have much lower risks of developing Kaposi sarcoma compared to solid organ transplant patients

**Kaposi Sarcoma (KS) Genomic DATA:**

* Etiologic Agent:  
  KS is caused by infection with Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8). The virus is necessary but not sufficient alone for KS development; additional host and viral factors contribute.
* Viral Genomic Variations:
  + Studies of KSHV genomes from KS tumors reveal frequent genomic rearrangements and mutations in viral genes, especially:
    - K5-K6 region over-representation (gene amplification)
    - K8.1 gene inactivation in some tumors
    - Mutations in miR-K10 microRNA coding sequence, potentially linked to tumor behavior and survival outcomes.
  + These viral mutations often arise de novo and may correlate with clinical features like tumor type and lesion distribution.
* Host Genetic Factors and Mutations:
  + Host oncogenes and tumor suppressor genes implicated in KS progression include:
    - TP53 (tumor suppressor) alterations
    - c-myc amplification and expression in some cases
    - Mutations or polymorphisms in KRAS, IL-6 promoter, and p53 codon 72 polymorphism have been studied, but their exact roles remain under investigation.
  + No consistent integration of HHV-8 into the host genome has been observed.
* Viral Latency Genes and Oncogenesis:
  + KSHV expresses latency genes such as LANA, v-cyclin (v-cyc D), v-FLIP, and Kaposin, which promote cell proliferation and inhibit apoptosis, contributing to KS tumorigenesis.
* Genetic Susceptibility:
  + Rare familial cases of classic KS have been linked to germline variants in genes like WAS, IFNGR1, STIM1, and TNFRSF4 (OX40), suggesting host genetic predisposition in some individuals.

## **ACTG TIS Staging System**

This system evaluates three key factors, each classified as good risk (0) or poor risk (1):

| **Factor** | **Good Risk (0)** | **Poor Risk (1)** |
| --- | --- | --- |
| Tumor (T) | Confined to skin and/or lymph nodes, minimal oral disease | Tumor-associated edema or ulceration, extensive oral KS, or visceral involvement |
| Immune system (I) | CD4 count ≥ 200 cells/mm³ | CD4 count < 200 cells/mm³ |
| Systemic illness (S) | No history of opportunistic infections or “B” symptoms (fever, weight loss, night sweats) | Presence of opportunistic infections or “B” symptoms |

* Early-stage KS (Good risk): T0I0S0
* Advanced-stage KS (Poor risk): Any combination with one or more poor risk features (e.g., T1I0S0, T0I1S0, T1I1S1, etc.)

Procedures and Treatment Timelines

## 1. Initial Evaluation and Diagnosis

* Timeline: Days to 1–2 weeks
* Includes physical exam, biopsy of lesions, imaging (if internal involvement suspected), and HIV testing if relevant.

## 2. Treatment Options for Localized Skin Lesions

* Radiation Therapy
  + Effective for solitary or limited lesions.
  + Typical regimen:
    - Electron beam radiation: 4 Gy once weekly for 6–8 weeks, or
    - Low-voltage photon radiation: 8–10 Gy single dose or 15–20 Gy over 1 week.
  + Timeline: Treatment spans 1–2 months depending on fractionation.
  + Excellent local control but recurrence in adjacent untreated skin is possible.
* Surgical Excision
  + Suitable for small, superficial lesions.
  + Multiple excisions may be needed due to recurrence.
  + Timeline: Usually outpatient procedure with recovery in days to weeks.
* Cryotherapy and Laser Therapy
  + Used for small lesions (≤1 cm), especially in acral areas.
  + Sessions last 30–60 seconds, repeated as needed.
  + Timeline: Can be repeated every few weeks.
* Intralesional Therapy
  + Injection of chemotherapy agents like vinblastine or interferon alfa.
  + Given every 2 weeks for several cycles (e.g., 4–6 treatments).
  + Timeline: Typically 1–3 months.
* Topical Therapy
  + Alitretinoin gel or imiquimod cream applied over weeks to months.

## 3. Treatment for Disseminated or Extensive Disease

* Highly Active Antiretroviral Therapy (HAART)
  + For HIV-associated KS, initiation or optimization of HAART is critical.
  + Can lead to lesion regression over weeks to months.
  + Timeline: Lifelong therapy, with clinical improvement often seen within 2–3 months.
* Systemic Chemotherapy
  + Liposomal doxorubicin is first-line for extensive disease.
  + Paclitaxel, vinblastine, bleomycin, or etoposide are alternatives.
  + Administered intravenously every 2–3 weeks for multiple cycles (usually 4–6 cycles).
  + Timeline: Treatment spans several months; response assessed periodically.
* Immunotherapy and Targeted Therapies
  + Emerging options in clinical trials; timelines vary.

## 4. Follow-Up and Monitoring

* Regular follow-up every 3–6 months to monitor for recurrence or progression.
* Imaging and clinical exams as indicated.

**Doctor-patient conversation about Kaposi sarcoma (KS),**

Doctor: I want to talk with you about your diagnosis of Kaposi sarcoma. This is a rare type of cancer that affects the blood vessels and can cause lesions on the skin and sometimes inside the body.

Patient: What causes Kaposi sarcoma? Is it contagious?

Doctor: Kaposi sarcoma is caused by a virus called human herpesvirus 8 (HHV-8). It’s not contagious like a cold or flu. Usually, KS develops in people whose immune systems are weakened, such as those with HIV/AIDS or who are on immunosuppressive medications.

Patient: What symptoms should I expect, and is it serious?

Doctor: KS often starts as purple or red spots or bumps on the skin, which may or may not cause discomfort. It can also affect lymph nodes and internal organs in some cases. The seriousness depends on how widespread the lesions are and your overall health, especially your immune status.

Patient: How do you confirm the diagnosis?

Doctor: We confirmed it with a biopsy of one of your skin lesions. Additional tests like blood work and imaging may be done to check if the disease has spread internally.

Patient: What treatments are available?

Doctor: Treatment depends on the extent of your KS and your immune function. For limited skin lesions, options include local therapies like radiation, cryotherapy, or surgery. If the disease is more widespread or internal, systemic treatments such as chemotherapy or immunotherapy may be needed. For patients with HIV, starting or optimizing antiretroviral therapy is crucial.

Patient: What side effects should I expect from treatment?

Doctor: Side effects vary by treatment. Radiation can cause skin irritation and fatigue; chemotherapy may cause nausea, hair loss, and lowered immunity. Antiretroviral therapy helps improve immune function but can have side effects like nausea or fatigue. We will monitor you closely and manage any side effects.

Patient: Will I be able to continue my normal activities?

Doctor: Many patients continue daily activities during treatment, though you may need to adjust based on how you feel. Fatigue is common, so rest is important. We will support you throughout.

Patient: Should I see any other specialists?

Doctor: Yes, it’s important to work with an infectious disease specialist, especially if you have HIV, as well as dermatologists and oncologists experienced in KS.

Patient: What is the outlook for someone with KS?

Doctor: Prognosis varies widely. Many patients do well with treatment, especially if their immune system improves. Regular follow-up is essential to monitor for new lesions or progression.

Patient: Are there resources I can read or support groups I can join?

Doctor: Absolutely. I can provide brochures and recommend websites like the American Cancer Society and HIV.gov. Support groups for KS and HIV patients can also be very helpful.

Patient: What happens if I decide not to treat it?

Doctor: Without treatment, KS lesions may grow and spread, potentially causing swelling, pain, or organ problems. It’s best to start treatment early to control the disease and maintain quality of life.

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**EWING SARCOMA**

**DEFINITION AND DESCRIPTION**

Ewing sarcoma is a type of cancer that begins as a growth of cells in the bones and the soft tissue around the bones. Ewing (Yoo-ing) sarcoma mostly happens in children and young adults, although it can happen at any age.

Ewing sarcoma most often begins in the leg bones and in the pelvis, but it can happen in any bone. Less often, it starts in the soft tissues of the chest, abdomen, arms or other locations.

Major advances in the treatment of Ewing sarcoma have improved the outlook for this cancer. Young people diagnosed with Ewing sarcoma are living longer. They sometimes face late effects from the strong treatments. Healthcare professionals often suggest long-term monitoring for side effects after treatment.

**Symptoms**

Ewing sarcoma signs and symptoms typically start in and around a bone. This cancer most often affects bones in the legs and the pelvis.

When symptoms happen in and around a bone, they might include:

* A lump in the arm, leg, chest or pelvis.
* Bone pain.
* Break in a bone, also called a fracture.
* Pain, swelling or tenderness near the affected area.

Sometimes Ewing sarcoma causes symptoms that affect the whole body. These can include:

* Fever.
* Losing weight without trying.
* Tiredness.

**When to see a doctor**

Make an appointment with a healthcare professional if you or your child has ongoing signs and symptoms that worry you.

**Causes**

It is not clear what causes Ewing sarcoma.

Ewing sarcoma happens when cells develop changes in their DNA. A cell's DNA holds the instructions 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.

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 is called metastatic cancer.

In Ewing sarcoma, the DNA changes most often affect a gene called *EWSR1*. If your healthcare professional suspects that you or your child has Ewing sarcoma, the cancer cells may be tested to look for changes in this gene.

**Risk factors**

Risk factors for Ewing sarcoma include:

* **Young age.** Ewing sarcoma can happen at any age. But it is more likely to happen in children and young adults.
* **European ancestry.** Ewing sarcoma is more common in people of European ancestry. It's much less common in people of African and East Asian ancestry.

There's no way to prevent Ewing sarcoma.

**Complications**

Complications of Ewing sarcoma and its treatment include the following.

**Cancer that spreads**

Ewing sarcoma can spread from where it started to other areas. Ewing sarcoma most often spreads to the lungs and to other bones.

**Long-term treatment side effects**

The strong treatments needed to control Ewing sarcoma can cause major side effects, both in the short and long term. Your healthcare team can help you 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.

**Diagnosis**

Ewing sarcoma diagnosis usually begins 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 a Ewing sarcoma. 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**

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.

A biopsy is needed to confirm a Ewing sarcoma diagnosis. Your healthcare team uses this information to make a treatment plan.

**Testing the cancer cells for DNA changes**

A sample of the cancer cells will be tested in the lab to find which DNA changes are in the cells. Ewing sarcoma cells mostly have changes in the *EWSR1* gene. Most often the *EWSR1* gene joins with another gene called *FLI1*. This creates a new gene called *EWS-FLI1*.

Testing the cancer cells for these gene changes can help confirm your diagnosis.

**Treatment**

Ewing sarcoma treatment most often includes chemotherapy and surgery. Which treatment you have first will depend on your situation. Other treatment options might include radiation therapy and targeted therapy.

**Chemotherapy**

Chemotherapy treats cancer with strong medicines.

Chemotherapy is sometimes used as the first treatment for Ewing sarcoma. The medicines may shrink the cancer. That makes it easier to remove the cancer with surgery or target with radiation therapy.

After surgery or radiation therapy, chemotherapy treatments might be used to kill any cancer cells that might remain.

For advanced cancer that spreads to other areas of the body, chemotherapy might help relieve pain and slow the growth of the cancer.

**Surgery**

The goal of surgery is to remove all the cancer cells. Surgery for Ewing sarcoma might mean removing a small portion of bone and some surrounding tissue. Rarely, it might mean removing the affected arm or leg.

Surgery on an arm or leg might affect the way you can use that limb. Surgeons carefully plan the surgery to minimize this risk, when possible.

Whether surgeons can remove all the cancer without removing the arm or leg depends on several factors. These include the size of the cancer, where it is and whether chemotherapy helps shrink it.

**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 you. The machine directs radiation to precise points on your body.

Radiation therapy might be suggested after surgery to kill cancer cells that remain. Radiation therapy might be used instead of surgery if an operation is not possible or if it is likely to hurt nearby organs. For example, if the surgery might cause loss of bowel or bladder control, radiation might be used instead.

For advanced Ewing sarcoma, radiation therapy can slow the growth of the cancer and help relieve pain.

**Targeted therapy**

Targeted therapy for cancer is a treatment that uses medicines that attack specific ways that cancer cells can grow. By blocking these specific things in the cells, targeted treatments can cause cancer cells to die. For Ewing sarcoma, researchers are looking at using targeted therapy when the cancer comes back or does not respond to other treatments.

## **Outlook / Prognosis**

Your child’s prognosis, or expected outcome, depends on several factors, like:

* Your child’s age at diagnosis. Kids diagnosed before age 10 may have better prognoses than older kids and teenagers.
* Where the tumor started. Tumors that start in arms and legs are easier to treat than tumors in their spine and pelvis.
* The tumor’s size. Smaller tumors are easier to treat than larger tumors.
* Whether the tumor metastasized or spread by the time it was diagnosed.

#### **What is the survival rate for Ewing sarcoma?**

Ewing sarcoma survival rates vary depending on factors like a child’s age and whether cancerous tumors spread before diagnosis. Based on age, 78% of kids under age 15 and 68% of teenagers ages 15 to 19 were alive five years after diagnosis.

Survival rates based on tumor location at diagnosis are:

* An estimated 82% of people with localized tumors were alive five years after diagnosis. Localized tumors are tumors diagnosed before they spread from the area where they started.
* An estimated 71% of people with regional tumors were alive five years after diagnosis. Regional tumors include tumors that spread to nearby tissues before being diagnosed.
* An estimated 39% of people with metastatic tumors were alive five years after diagnosis. Ewing sarcoma tumors may spread to lungs, other bones or bone marrow.

It’s important to remember that Ewing sarcoma survival rates are estimates based on other people’s experiences with the condition. Their situations may be very different from yours. If you have questions, ask your healthcare provider to explain your or your child’s prognosis.

## **Prevention**

There’s no known way to prevent Ewing sarcoma.

## **Living With**

In a way, your child will be living with Ewing sarcoma for the rest of their life. That’s because late effects from cancer treatment can develop years after your child completes treatment. You can help your child by:

* Ensuring they have regular follow-up appointments after treatment.
* Encouraging them to develop good self-care habits, like having a healthy diet and getting exercise.
* Encouraging them to avoid activities, like smoking, that increase their risk of developing cancer again.

#### **My child has Ewing sarcoma. What can I do to help them cope?**

Ewing sarcoma typically happens around the time children start puberty. Puberty may feel like you and your teenager are on an emotional rollercoaster with sudden and unexpected twists and turns. A cancer diagnosis may put that emotional rollercoaster into overdrive.

Apart from feeling anxious about their health and coping with side effects, teenagers with Ewing sarcoma may feel frustrated about missing out on everyday activities at school and with friends. They may feel self-conscious about treatment side effects like losing hair. If that’s your family situation, talking with your child may help.

Cancer can turn family life upside down, particularly if it’s cancer in your child. If you or your child are feeling overwhelmed, reach out to the child life specialist on your child’s care team. They’ll give you and your child helpful support and information.

You should go to the emergency room if your child has an unusually strong reaction to treatment. For example, some treatment side effects include nausea and diarrhea. You should also take your child to the emergency room if you’re concerned they’re dehydrated.

## **Diagnostic Considerations**

Because Ewing sarcomas are rare, they are often not considered in a differential diagnosis until biopsy reveals a neoplasm known as a small round blue cell tumor. Malignancy is usually in the differential diagnosis before biopsy. For this reason, consultation with a pediatric oncologist is critical.

Ewing sarcoma should be considered in the differential diagnosis if a patient aged 10-30 years has a soft tissue or bony mass that causes the physician to consider the presence of a neoplasm.

## **Differential Diagnoses**

* Nonrhabdomyosarcoma Soft Tissue Sarcomas
* Pediatric Neuroblastoma
* Pediatric Non-Hodgkin Lymphoma
* Pediatric Osteomyelitis
* Pediatric Osteosarcoma
* Pediatric Rhabdomyosarcoma
* Rickets

## **Epidemiology**

### United States statistics

The overall annual incidence of Ewing sarcoma is approximately 1 case per 1 million per year in the United States. The incidence from birth to age 20 years is 2.9 cases per million population. Approximately half of all patients are aged 10-20 years at the time of first diagnosis, making this the second most common primary malignant bone tumor in children and adolescents. Cases have been reported from birth through 80 years, although very infrequently.

### Race-, sex-, and age-related demographics

The incidence of these tumors in Whites is at least 9 times higher than it is in Blacks. This finding contrasts with that observed in osteosarcoma, which has a relatively equal racial distribution. African countries report similar incidences, with a paucity of Ewing sarcoma.

The incidence of Ewing sarcoma in females is 2.6 cases per million population, compared with 3.3 cases per million population in males.

The incidence of these tumors peaks in the late teenage years. Overall, 27% of cases occur in the first decade of life, 64% of cases occur in the second decade, and 9% of cases occur in the third decade.

**STAGING**

* T (Tumor size and extent):
  + T1: Tumor ≤ 8 cm (some sources use 5 cm cutoff)
  + T2: Tumor > 8 cm and ≤ 10 cm (or >5 cm in some systems)
  + T3: More than one tumor in the same bone
  + T4: Tumor > 15 cm (in some soft tissue sarcoma staging)
* N (Lymph node involvement):
  + N0: No regional lymph node metastasis (rare in Ewing sarcoma)
  + N1: Regional lymph node metastasis present
* M (Distant metastasis):
  + M0: No distant metastasis
  + M1a: Metastasis to lungs only
  + M1b: Metastasis to other distant sites (bone, bone marrow, liver, etc.)
* G (Grade):
  + All Ewing sarcomas are high grade (G3).

## AJCC Stage Groupings

| **Stage** | **Description** |
| --- | --- |
| 1A | T1 N0 M0 G1 or GX (low grade; rarely used for Ewing sarcoma since all are high grade) |
| 1B | T2 or T3 N0 M0 G1 or GX (low grade; rarely used for Ewing sarcoma) |
| 2A | T1 N0 M0 G2 or G3 (tumor ≤ 8 cm, no nodes, no metastasis, high grade) |
| 2B | T2 N0 M0 G2 or G3 (tumor > 8 cm, no nodes, no metastasis, high grade) |
| 3 | T3 N0 M0 G2 or G3 (multiple tumors in same bone, no nodes, no metastasis, high grade) |
| 4A | Any T N0 M1a Any G (metastasis to lungs only) |
| 4B | Any T N1 Any M Any G or Any T Any N M1b Any G (lymph node involvement or distant metastasis beyond lungs) |

**Genomic Data of Ewing Sarcoma**

* Ewing sarcoma is primarily driven by characteristic chromosomal translocations that fuse the EWSR1 gene (on chromosome 22) with an ETS family transcription factor gene (most commonly FLI1 on chromosome 11), creating oncogenic fusion proteins (e.g., EWSR1-FLI1) that act as aberrant transcription factors initiating tumorigenesis.  
  Secondary Genetic Alterations and Mutation Landscape
  + Low overall mutation burden:  
    Ewing sarcoma tumors have a relatively low number of somatic mutations compared to many other cancers, with an average tumor mutation burden (TMB) < 10 mutations/Mb.
  + Common recurrent mutations:
    - STAG2 mutations (~17–22%): A cohesin complex subunit gene, frequently mutated or lost; associated with worse prognosis and tumor progression.
    - CDKN2A deletions (~12–14%): Tumor suppressor gene loss, mutually exclusive with STAG2 mutations.
    - TP53 mutations (~6–7%): Tumor suppressor gene mutations linked to poor outcome; often co-occur with STAG2 mutations.
    - Other less frequent mutations include EZH2, BCOR, ZMYM3, and ERF.
  + Mutations in DNA repair and cell cycle genes:
    - Genes involved in DNA repair pathways such as ATR, BRCA1, RAD50, ATM, CHEK1, NBN show mutations, especially in pediatric patients.
    - Mutations in PIK3R1 (59% in one study) and POLE (50%) have been reported, with some variation by age group.

### **What questions should I ask my doctor?**

## **What type of Ewing tumor does my child have?**

Ewing sarcoma is a rare, aggressive cancer that usually arises in bone or soft tissue. It is characterized by a specific genetic fusion (most commonly EWSR1-FLI1) and is classified as a high-grade small round blue cell tumor. Your child’s care team will confirm the diagnosis through biopsy, imaging, and molecular testing.

## 2. **What stage is the cancer? What does this mean?**

Staging depends on tumor size, location, lymph node involvement, and whether the cancer has spread (metastasized).

* Localized disease means the tumor is confined to one area.
* Metastatic disease means the cancer has spread to other parts of the body (commonly lungs or other bones).  
  Staging guides treatment decisions and helps predict prognosis. Early-stage tumors generally have better outcomes.

## 3. **What treatment plan do you recommend and why?**

Treatment usually involves a multimodal approach:

* Chemotherapy first (neoadjuvant): to shrink the tumor and treat any microscopic spread.
* Surgery and/or radiation therapy: to remove or destroy the primary tumor. Surgery aims for limb-sparing procedures when possible.
* Additional chemotherapy (adjuvant): after local control to kill remaining cancer cells.
* In some cases, high-dose chemotherapy with stem cell transplant may be considered for high-risk disease.  
  Your child’s team will tailor the plan based on tumor size, location, and overall health.

## 4. **What’s the goal of each treatment? Is it to eliminate the cancer, help my child feel better or both?**

* Chemotherapy: aims to destroy cancer cells throughout the body and shrink the tumor.
* Surgery/radiation: aims to eliminate the primary tumor locally.
* The overall goal is curative—to eliminate cancer completely. Supportive care during treatment also focuses on symptom relief and maintaining quality of life.

## 5. **What are the possible side effects of each treatment, both in the short term and long term?**

* Chemotherapy: short-term—nausea, hair loss, fatigue, increased infection risk; long-term—potential effects on heart, fertility, growth, and risk of secondary cancers.
* Surgery: pain, infection risk, possible functional impairment depending on tumor site, but limb-sparing techniques minimize disability.
* Radiation therapy: skin irritation, fatigue; long-term—growth disturbances, secondary malignancies, tissue fibrosis.
* Stem cell transplant: intensive treatment with risks of infection, organ toxicity, and longer recovery.

## 6. **How will treatment affect my child’s daily life? Will they be able to go to school and perform their usual activities?**

Treatment can cause fatigue and other side effects that may limit activities. Many children continue some schooling and social activities with accommodations. Your care team will help balance treatment and normal life, providing support as needed.

## 7. **Will surgery be necessary?**

Often, yes. Surgery is usually recommended to remove the tumor after chemotherapy shrinks it, especially if it can be done safely with limb-sparing techniques.

## 8. **What type of surgery do you recommend and why?**

Limb-salvage surgery is preferred to remove the tumor while preserving limb function. Amputation is rare and reserved for cases where limb-sparing is not feasible.

## **10. What’s the chance that the cancer will come back? Should I watch for specific signs or symptoms?**

The risk of recurrence depends on initial stage and response to treatment. Regular follow-up visits and imaging are essential. Watch for new pain, swelling, lumps, or unexplained symptoms and report them promptly.

## 11. **Is there anything my child can do to reduce their risk of getting another type of cancer?**

There are no guaranteed ways to prevent secondary cancers, but minimizing exposure to unnecessary radiation, following up regularly, and maintaining a healthy lifestyle can help reduce risks.

## 1**2. What follow-up tests will my child need, and how often will they need tests?**

Follow-up typically includes:

* Physical exams and imaging (X-rays, MRI, CT, or PET scans) every 3–6 months initially, then less frequently over time.
* Blood tests to monitor general health.
* Long-term monitoring for late effects of therapy.

**Doctor-patient conversation about Ewing sarcoma in a child,**

Doctor: I understand this is a very difficult time for you and your family. I want to explain what we know about your child’s diagnosis of Ewing sarcoma and what the next steps are.

Parent: Thank you. What exactly is Ewing sarcoma?

Doctor: Ewing sarcoma is a rare type of cancer that usually starts in the bones but can also arise in soft tissues. It most commonly affects children and teenagers. It is caused by a specific genetic change in the tumor cells, which we confirmed through the biopsy.

Parent: What stage is the cancer? What does that mean for my child?

Doctor: Staging tells us how far the cancer has spread. If it’s localized, meaning it’s only in one area, the chances of successful treatment are better — about 70 to 75% survival for localized disease. If it has spread to other parts of the body, like the lungs or other bones, treatment is more complex, but many children still respond well.

Parent: What treatment do you recommend?

Doctor: We typically start with chemotherapy to shrink the tumor and treat any cancer cells that might have spread microscopically. After that, we’ll plan surgery to remove the tumor if possible, ideally using limb-sparing techniques to preserve function. Sometimes radiation is used instead of or in addition to surgery. After local treatment, we continue chemotherapy to reduce the risk of recurrence.

Parent: What are the goals of these treatments?

Doctor: Our goal is to cure the cancer — to eliminate it completely. We also want to help your child feel as comfortable as possible during treatment and maintain their quality of life.

Parent: What side effects should we expect?

Doctor: Chemotherapy can cause nausea, hair loss, fatigue, and increased risk of infection in the short term. Long-term effects can include impacts on heart function, fertility, or growth, but we monitor closely and provide supportive care. Surgery may cause pain and require rehabilitation, but we aim to preserve as much function as possible.

Parent: How will this affect my child’s daily life? Will they still be able to go to school?

Doctor: Many children continue some schooling and activities during treatment, though they may need to take breaks and have accommodations. Fatigue is common, so rest is important. We have a team including physical therapists and psychologists to support your child.

Parent: Will surgery definitely be needed?

Doctor: Usually, yes, after chemotherapy shrinks the tumor. We prefer limb-sparing surgery to avoid amputation whenever possible.

Parent: Are there clinical trials available?

Doctor: Yes, there are ongoing trials testing new chemotherapy combinations, targeted therapies, and supportive care approaches. I can provide information on trials suitable for your child and help with enrollment if you’re interested.

Parent: What’s the chance the cancer will come back? How will we know?

Doctor: The risk depends on the initial stage and response to treatment. We’ll schedule regular follow-ups with exams and imaging to monitor for recurrence. Watch for new pain, swelling, or lumps and report them promptly.

Parent: Is there anything my child can do to lower the risk of other cancers later?

Doctor: While we can’t guarantee prevention, maintaining a healthy lifestyle and avoiding unnecessary radiation exposure helps. We’ll also monitor your child long-term for any late effects.

Parent: What kind of follow-up will my child need?

Doctor: Follow-up usually involves physical exams and imaging every 3–6 months initially, then less frequently over time. We also monitor for late effects of treatment.

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**FIBROSARCOMA**

**DEFINITION AND DESCRIPTION**

Fibrosarcoma is a rare soft tissue cancer (sarcoma). If you develop fibrosarcoma, you have a soft tissue tumor in the connective tissues that keep parts of your body together. These tissues include tendons and ligaments. Sometimes, fibrosarcoma forms inside bones or in fibrous connective tissue covering bone.

Fibrosarcoma most often forms in soft tissue deep inside your leg (especially your shin bone or thigh bone), upper arm, knees or trunk. Less often, they start in your head or neck.

If you or your child is diagnosed with fibrosarcoma, what comes next depends on lots of things — from your age to the tumor’s size and location. Your healthcare provider will explain what to expect based on your diagnosis.

**Types**

There are two types of fibrosarcoma. They’re very different:

* **Infantile (congenital) fibrosarcoma**. This type usually presents at birth or shortly after. It grows fast but rarely spreads. It’s usually curable.
* **Adult-type fibrosarcoma**. This type is most common in adults between 20 and 60. But it can also affect older children and adolescents. Unlike the infantile type, adult-type fibrosarcoma is typically more aggressive and harder to treat.

Fibrosarcoma is rare in both adults and children. The adult type accounts for approximately 10% of soft tissue sarcoma diagnosis. Infantile fibrosarcoma is one of the most common sarcomas diagnosed in children under 5, but it’s still rare overall. It affects fewer than 5 out of 1 million infants.

**Symptoms and Causes**

It usually takes time for fibrosarcoma symptoms to surface. Because fibrosarcoma develops in deep soft tissues, you might not notice any changes in your body until the tumor grows bigger and presses on a nerve or blood vessel.

Typical symptoms of fibrosarcoma include:

* A painless or tender soft lump in your legs, arms or trunk.
* Tingling or “pins and needles” feeling or sharp, aching or burning pain (this might be a sign of a pinched nerve near the tumor).
* Unusual swelling (this might be a sign the tumor is pressing on your blood vessels).

Fibrosarcoma symptoms can resemble symptoms of other, less serious conditions. Only a healthcare provider can determine whether the changes are because of a fibrosarcoma or a more common, benign (noncancerous) condition.

**What causes fibrosarcoma?**

Researchers haven’t pinpointed what causes fibrosarcoma, but genetic mutations (changes) in cells likely play a role. Many fibrosarcomas have the same changes in their cell DNA. These changes can cause cells to multiply rapidly and form cancerous tumors.

Medical experts have identified a common mutation in infantile fibrosarcoma. About 90% involve issues with the *NTRK* gene family (there are three *NTRK* genes). When these genes aren’t working as they should, tumors can form.

**Risk factors**

Researchers have identified some inherited conditions that might increase your risk of developing fibrosarcoma:

* Familial adenomatous polyposis
* Li-Fraumeni syndrome
* Neurofibromatosis type 1
* Nevoid basal cell carcinoma syndrome
* Retinoblastoma
* Tuberous sclerosis
* Werner syndrome

Other conditions associated with fibrosarcoma include:

* Bone infarction (lack of blood flow causes bone cells to die)
* Chronic (long-term) osteomyelitis
* Fibrous dysplasia
* Paget’s disease of the bone

Risk factors related to your environment and previous medical history include:

* Previous radiation therapy directed toward the area with the tumor
* Previous severe burn at the tumor site
* Exposure to certain chemicals, such as thorium dioxide, vinyl chloride or arsenic
* Exposure to certain metals in orthopedic implants, like chromium, cobalt or nickel

**Diagnosis and Tests**

Healthcare providers perform several tests when diagnosing fibrosarcoma. They’ll use what they learn to establish a stage and grade for your fibrosarcoma. Tests might include:

* **Magnetic resonance imaging (MRI)**. This is the most common imaging test for diagnosing fibrosarcomas. It can show a tumor’s size and location, and if it impacts blood vessels or nerves.
* **Computed tomography scan (CT scan)**. This test uses a series of X-rays and a computer to create 3D images of your soft tissues and bones.
* **Biopsy**. A provider may remove tissue from the lump (core needle biopsy), or they may cut it out entirely (excisional biopsy). A pathologist will check the tissue for cancer cells in a lab.
* **Immunohistochemistry (IHC)**. This lab test uses proteins called antibodies to determine whether a tumor is a fibrosarcoma or a different type of soft tissue tumor.

**Stages of fibrosarcoma**

Healthcare providers stage fibrosarcoma to determine how advanced it is. Your provider will consider the tumor’s size, location and if it’s spread. They’ll also grade the cancer, which is based on how abnormal the cells look under a microscope. Tumors with abnormal-looking cells are “high” grade and tend to be more aggressive.

The stages of fibrosarcoma are:

* **Stage I**: Low-grade fibrosarcomas. More advanced Stage I tumors are bigger than 5 centimeters (cm).
* **Stage II**: Mid-grade or high-grade fibrosarcomas. More advanced Stage II tumors are bigger than 5 cm.
* **Stage III**: High-grade fibrosarcomas. Stage III tumors are larger than 5 cm and have spread to nearby lymph nodes.
* **Stage IV**: Fibrosarcomas of any grade or size that have spread to distant organs or tissue.

Your provider will explain how the cancer stage will impact your prognosis, or likely outcome following treatment.

**Management and Treatment**

Fibrosarcoma treatment depends on lots of factors, including your overall health, preferences and the tumor type.

For adult-type fibrosarcoma, healthcare providers typically use:

* **Surgery**. During surgery, providers remove the tumor and a margin of healthy tissue to ensure no cancer cells remain.
* **Radiation therapy**. You may need radiation therapy before surgery to shrink the tumor or afterward to destroy any remaining cancer cells.
* **Chemotherapy**. Although some providers prescribe chemotherapy, results are mixed when it comes to this treatment. Chemotherapy doesn’t work on most adult-type fibrosarcomas.

For infantile fibrosarcoma, surgery to remove the tumor is often curative. Your healthcare provider may also recommend:

* **Radiation and/or chemotherapy**. These treatments can shrink tumors before surgery or destroy any remaining cancer cells after surgery. Unlike the adult type, most infantile-type fibrosarcomas respond well to chemotherapy.
* **Targeted therapy**. This treatment can stop cells from dividing too fast because of problems with the *NTRK* genes. It can shrink tumors, making surgery easier.

**Outlook / Prognosis**

The outlook for infantile-type fibrosarcomas is excellent. Most are curable with a combination of surgery, radiation chemotherapy or targeted therapy.

The outlook is more complex with adult-type fibrosarcomas. Many tumors aren’t diagnosed until they’ve grown large enough to be noticeable, soft lumps that affect your nerves or circulation. Like many types of cancer, early diagnosis can lead to a better outcome. Fibrosarcoma is much harder to treat once it’s advanced. About half return after treatment.

Still, many factors affect your prognosis. Some factors, like your age and overall health, are unique to you. Others, like the tumor stage and grade, depend on the fibrosarcoma.

Ask your healthcare provider what factors impact your prognosis.

**What is the survival rate for fibrosarcoma?**

Between 40% and 60% of people who have adult-type fibrosarcoma are alive five years after diagnosis. Researchers are investigating several new ways to slow fibrosarcoma’s growth.

The 10-year survival rate for infantile-type fibrosarcoma is 90%. That number is closer to 100% if surgery successfully removes all traces of the cancer.

**Prevention**

You can’t prevent fibrosarcoma. But understanding your biological family’s medical history may help with early diagnosis and treatment. Fibrosarcoma appears to be related to some inherited conditions. If your family has a history of one of those conditions, ask your healthcare provider about monitoring your health for signs of this condition.

**Living With**

Often, a cancer diagnosis makes people feel powerless. Committing to self-care during and after cancer treatment is one way to manage those feelings. Here are some things you can do:

* **Understand your follow-up care plan**. Ask your healthcare provider what to expect when it comes to your recovery and follow-up appointments. Knowing what comes next can keep your focus on what you can control rather than what you can’t.
* **Address anxiety**. Regular checkups and tests after treatment are an important part of catching a recurrence (cancer coming back). But they can cause anxiety, too. Speak to a therapist for help managing anxiety.
* **Ask for help**. You’ll probably need help while you’re going through treatment. Your loved ones are likely anxious to do what they can. Let them know how they can help you.
* **Focus on wellness**. Eating nutritious foods, getting adequate physical activity and logging enough hours of sleep each night is just as important with a cancer diagnosis as without.
* **Rest**. Cancer and cancer treatments can leave you feeling exhausted. Plan to rest as much as possible during your treatment.
* **Combat stress**. Cancer is stressful. Activities like meditation, relaxation exercises and deep breathing exercises can help ease stress.

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

Most people see their providers every three months for the first two years after treatment and then at longer intervals until four or five years after treatment. This timeline helps providers detect any recurrences immediately. When fibrosarcoma comes back, it usually does so within the first five years.

You should always contact your provider any time you notice new lumps or have new pain. While lumps and pain might not be cancer, you should see your provider so they can check your symptoms.

Many cancer treatments affect your immune system, increasing your chance of developing infections. Symptoms that might require an emergency room visit during treatment include:

* Fever of 100.4 degrees Fahrenheit (38.3 degrees Celsius) and above
* Chills
* Productive or “wet” cough
* Stomach pain
* Persistent diarrhea
* Persistent nausea and vomiting

## 

## **Diagnostic Considerations**

Differential diagnoses include the following:

* Fibrous dysplasia
* Fibrous histiocytoma
* Osteosarcoma
* Paget sarcoma
* Malignant fibrous histiocytoma
* Malignant neurosarcoma

## 

## **Epidemiology**

Fibrosarcoma represents only about 10% of musculoskeletal sarcomas and fewer than 5% of all primary tumors of bone. It can be diagnosed in patients of any age, but it is diagnosed more commonly in patients in the fourth decade of life. It is usually located in the lower extremities, especially the femur and tibia.

Fibrosarcoma of the soft tissues usually affects a wider age spectrum of patients than fibrosarcoma of the bone does, with an age range of 35-55 years. It often arises in the soft tissues of the thigh and the posterior knee. It is generally a large, painless mass deep to fascia and has an ill-defined margin.

An infantile form (in children < 10 years) of fibrosarcoma exists. Unlike fibrosarcoma in adults, it has an excellent prognosis—even in the face of metastatic disease at presentation—when treated with a combination of neoadjuvant and adjuvant chemotherapy and resection.

Fibrosarcoma of bone occurs slightly more commonly in men than in women. No known racial predilection exists.

**procedures and timeline are as follows:**

## 1. Diagnosis and Staging

* Initial imaging (MRI, CT) and biopsy to confirm diagnosis and assess tumor size, grade, and spread.
* Staging determines treatment plan and prognosis.

## 2. Surgery (Primary Treatment)

* Wide surgical resection with tumor-free margins (R0 resection) is the mainstay of treatment for localized fibrosarcoma.
* Surgery aims to remove the tumor along with some normal tissue to reduce local recurrence risk.
* For tumors in limbs, limb-sparing surgery is preferred; amputation is rare but may be necessary if vital structures are involved.
* In cases of intramuscular tumors, compartmental resection may be performed.
* Surgery timing depends on tumor size and patient's condition but usually occurs soon after diagnosis and staging.

## 3. Radiation Therapy

* May be given preoperatively (neoadjuvant) to shrink the tumor and facilitate surgery.
* Or postoperatively (adjuvant) to destroy residual microscopic disease, especially for high-grade, large (>5 cm), or deep tumors.
* Proton therapy is an option in some centers to minimize damage to surrounding tissues.
* Radiation is typically scheduled around surgery, either weeks before or after.

## 4. Chemotherapy

* Used variably depending on tumor grade, stage, and presence of metastases.
* Neoadjuvant chemotherapy (e.g., MAID regimen: mesna, doxorubicin, ifosfamide, dacarbazine) may be employed for high-grade tumors to improve surgical outcomes.
* Adjuvant chemotherapy after surgery is controversial but may be considered in advanced or metastatic disease.
* Chemotherapy agents include doxorubicin, ifosfamide, actinomycin D.
* Chemotherapy cycles are planned over weeks to months depending on regimen.

## 5. Follow-up and Supportive Care

* Regular imaging and clinical exams to monitor for recurrence.
* Physical and occupational therapy if surgery affects limb function.
* Pain management and rehabilitation as needed.

## Timeline Summary

| **Phase** | **Timing** | **Purpose** |
| --- | --- | --- |
| Diagnosis & Staging | Weeks 0-2 | Confirm diagnosis, plan treatment |
| Neoadjuvant Therapy | Weeks 2-6 (if indicated) | Shrink tumor before surgery |
| Surgery | Weeks 6-8 | Remove tumor with wide margins |
| Adjuvant Radiation | Weeks 8-12 (post-surgery) | Eliminate residual cancer cells |
| Adjuvant Chemotherapy | Weeks 8-20 (if indicated) | Treat systemic disease or reduce recurrence |
| Rehabilitation | Post-surgery ongoing | Restore function and quality of life |
| Follow-up | Every 3-6 months initially | Detect recurrence early |

**GENOMIC DATA**

* The most frequent genetic aberrations in fibrosarcoma are copy number losses of CDKN2A/CDKN2B (found in about 80% of cases) and mutations in TP53 (around 60%). These genes are key tumor suppressors involved in cell cycle regulation and DNA damage response.
* Additional recurrent alterations include NF1 mutations or copy number losses, BAP1 copy number loss, TERT mutations, and SMAD4 mutations, each observed in a subset of cases (20-40% frequency). These mutations may contribute to tumor progression and represent novel areas for research.
* Fusion gene formation through chromosomal rearrangements (deletions, duplications, inversions, translocations) is a critical mechanism in fibrosarcoma pathogenesis, producing unique fusion proteins that disrupt normal cell proliferation and apoptosis pathways. Such fusion genes may serve as targets for precision therapies.
* In rare pediatric cases, such as ovarian fibrosarcoma, mutations in genes like DICER1 and NF1 have been reported, linking fibrosarcoma to hereditary cancer syndromes (e.g., DICER1 syndrome).
* Variants of uncertain significance (VUS) have been detected in genes like NOTCH, FANCA, FANCD2, and PTCH1, but their roles in fibrosarcoma remain unclear and require further study

**DOCTOR PATIENT CONVERSATION**

DOCTOR: Good morning, Thanks for coming in. I know this has been a lot to process since we got the biopsy results last week. How are you feeling today?

PATIENT: Morning, Honestly, a bit overwhelmed. "Fibrosarcoma"... it's a scary word. I've been trying to read up, but it's a lot.

DOCTOR: I completely understand. It's a significant diagnosis, and it's natural to feel that way. Let's break it down together. My goal today is to explain what fibrosarcoma is, what we know about yours specifically, and then walk you through the treatment plan we’ve put together. Does that sound okay?

PATIENT: Yes, please. Just... try to keep it as simple as you can.

DOCTOR: Absolutely. So, fibrosarcoma is a rare type of cancer that originates in the fibroblasts, which are the cells that make up connective tissue in your body – things like muscles, ligaments, and fat. Think of it as a malignant tumor of these fibrous tissues. In your case, it's located in your upper thigh, correct?

PATIENT: That's right. The lump I felt. Is it aggressive?

DOCTOR: From the biopsy, we've identified it as a high-grade fibrosarcoma. "High-grade" means the cells appear more abnormal under the microscope, and they tend to grow and divide more quickly. This does suggest it's an aggressive type, which is why we need to act decisively.

PATIENT: So, what's the plan? Am I going to need chemo?

DOCTOR: We've reviewed your case with our multidisciplinary tumor board – that's a team of surgeons, radiation oncologists, and other specialists. For fibrosarcoma, the primary treatment is almost always surgery. The goal is to remove the entire tumor along with a margin of healthy tissue around it, to ensure we get all the cancer cells. This is called a "wide surgical resection."

PATIENT: And will that be enough?

DOCTOR: Potentially. However, given the size and the high-grade nature of your tumor, we also recommend radiation therapy. We have two main options for how to time that. We can either give you radiation before surgery, which is called neoadjuvant radiation. This aims to shrink the tumor, making it easier to remove and potentially reducing the extent of surgery. Or, we can give it after surgery, called adjuvant radiation, to clean up any microscopic cancer cells that might have been left behind, even after a successful surgery.

PATIENT: What's better? Before or after?

DOCTOR: That's a great question, and it's something we've discussed extensively. For your specific tumor, and considering its location, we're leaning towards neoadjuvant radiation first. Our surgeon believes that shrinking the tumor will allow for a more effective limb-sparing surgery – meaning we can avoid amputation and preserve more function in your leg. We want to maximize the chances of a complete removal while minimizing the impact on your quality of life.

PATIENT: So, radiation first, then surgery. What about chemotherapy? You mentioned chemo earlier.

DOCTOR: Good memory. Chemotherapy for fibrosarcoma is a bit more nuanced. It's not always used, especially for localized disease. However, for high-grade tumors like yours, especially if there's any concern about very small, undetectable spread (micrometastases), we sometimes consider adjuvant chemotherapy after surgery and radiation. This would be to try and target any cancer cells that might have traveled elsewhere in the body. We'll make a final decision on chemotherapy after we see how you respond to radiation and after the surgery, once we have a clearer picture from the removed tissue.

PATIENT: Okay... so, a general timeline? How long is all this going to take?

DOCTOR: Let's sketch that out. First, we'll get you set up for radiation planning. That usually involves a simulation scan.

* Radiation: This will likely be daily treatments, Monday through Friday, for about 5 to 6 weeks.
* Break: After radiation, we'll have a short break, perhaps 2-3 weeks, to allow your body to recover a bit before surgery.
* Surgery: Then, the surgical procedure itself. Recovery from that will vary, but you'll likely be in the hospital for a few days and then rehabilitation at home.
* Post-Surgery Recovery & Potential Chemo: After surgery, we'll assess the pathology. If chemotherapy is recommended, that would likely start a few weeks after you've recovered sufficiently from surgery, and those cycles can run for several months.

So, from start to finish, the active treatment phase could be anywhere from 6 to 9 months, depending on whether we proceed with chemotherapy and how quickly you recover.

PATIENT: That's... a long time. Will I be able to work? I'm a carpenter, you know.

DOCTOR: It will be challenging. During radiation, you'll likely feel fatigued, and there might be skin irritation in the treated area. After surgery, your mobility will be significantly impacted for a period, and you'll need physical therapy to regain strength and function. We'll work closely with you on managing symptoms and assessing your ability to work. We can get you connected with social workers and support groups who can help navigate these practical challenges. Our priority right now is getting rid of this cancer.

PATIENT: What are the risks of all this? The radiation, the surgery...?

DOCTOR: Good question. Each treatment has potential side effects.

* Radiation: Can cause skin changes (like a sunburn), fatigue, and potentially some swelling or stiffness in the muscles around the treated area. Long-term, there's a small risk of nerve damage or bone weakening in the treated field.
* Surgery: Risks include infection, bleeding, pain, and importantly, potential impact on leg function and mobility depending on how much tissue needs to be removed. We'll have a detailed discussion with the surgeon about the specifics of your operation.
* Chemotherapy (if needed): Common side effects include nausea, fatigue, hair loss, and a temporary drop in blood counts making you more susceptible to infection.

We will manage these side effects closely throughout your treatment. Your care team will be monitoring you every step of the way.

PATIENT: This is a lot to take in. My wife... can she come to the next appointment? I think she'd want to hear all this too.

DOCTOR: Absolutely, Rob. I encourage you to bring her. Having a second set of ears and emotional support is incredibly helpful. We can go over everything again. And please, write down any questions that come to mind between now and then. No question is too small.

PATIENT: Thank you, Dr. Sharma. I appreciate you explaining it so clearly. It helps, even though it's still... a lot.

DOCTOR: You're not alone in this, Rob. We have a very experienced team here, and we'll support you through every stage of your treatment. My nurse coordinator will be in touch today to schedule your radiation planning session and provide you with some additional written information. Take it one step at a time.

PATIENT: Okay. One step at a time. Thank you.

**What questions should I ask my healthcare provider?**

Questions you might want to ask include:

## **How advanced is fibrosarcoma**?

* Staging depends on tumor size, grade, depth, and spread.  
  High-grade fibrosarcomas larger than 5 cm and located deep in tissues are considered more advanced and carry a higher risk of local recurrence and metastasis.
* About 50% of high-grade sarcoma patients develop distant metastases, often to lungs, with median survival around 12-18 months after metastasis diagnosis.
* Accurate staging requires imaging and biopsy, and management is guided by tumor grade and size.

## 2. **What treatments do you recommend?**

* Primary treatment is wide surgical excision with clear margins to remove the tumor completely.
* For high-grade tumors >5 cm or deep location, adjuvant radiation therapy (pre- or post-operative) is strongly recommended to reduce local recurrence.
* Neoadjuvant (preoperative) radiation can shrink tumors to facilitate surgery and preserve function.
* Adjuvant chemotherapy is not routinely recommended but may be considered in selected high-risk cases or metastatic disease.
* For metastatic or unresectable disease, systemic chemotherapy (commonly doxorubicin, with or without ifosfamide) and palliative radiotherapy may be used.

## **3. Will I have a single treatment or more than one kind of treatment?**

* Most patients with high-grade fibrosarcoma receive multimodal treatment:
  + Surgery plus radiation therapy (either before or after surgery).
  + Chemotherapy may be added depending on tumor characteristics and spread.
* Treatment plans are individualized by a multidisciplinary sarcoma team.

## 4. **What’s the success rate for these treatments?**

* Surgery with radiation therapy achieves good local control, especially when wide margins are obtained.
* The 5-year survival for localized high-grade soft tissue sarcomas ranges approximately 50-60%, but varies by tumor size, grade, and metastasis.
* Metastatic disease has a poorer prognosis, with median survival around 12-18 months despite treatment.
* Early diagnosis and complete resection improve outcomes significantly.

## 5. What are the side effects of each treatment?

| **Treatment** | **Common Side Effects** |
| --- | --- |
| Surgery | Pain, infection, bleeding, wound healing issues, possible loss of limb function depending on extent. |
| Radiation | Skin irritation (like sunburn), fatigue, swelling, fibrosis (stiffness), possible nerve or bone damage long-term. Intensity-modulated radiation therapy (IMRT) reduces these risks. |
| Chemotherapy | Nausea, vomiting, fatigue, hair loss, lowered blood counts (infection risk), cardiac toxicity (doxorubicin), kidney toxicity (ifosfamide). |
| Palliative care | Symptom management side effects vary depending on treatments used. |

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**Dermatofibrosarcoma protuberans (DFSP)**

Dermatofibrosarcoma protuberans is a rare skin cancer that begins in your dermis, your skin’s middle layer. It’s pronounced “dur-MAT-toe-fy-bra-sar-CO-ma” “pro-TOO-bur-anz.” Your healthcare provider might call it DFSP.

This slow-growing cancer rarely spreads. Still, you need treatment to remove the tumor and prevent cancer from coming back (recurrence) or spreading (metastatic cancer). With proper treatment, DFSP has a high survival rate.

DFSP is a malignant (cancerous) soft tissue tumor and a type of skin cancer.

DFSP is a sarcoma (soft tissue tumor), cancer that develops in muscle, fat and skin. These tumors can also affect bones.

**Can DFSP metastasize (spread)?**

Cancer that spreads outside the original tumor is metastatic cancer. Approximately 1 in 20 people with DFSP experience cancer spread.

Metastatic DFSP is most likely to occur if you don’t get treatment or the cancer goes deep into fat and muscle.

For unknown reasons, DFSP can be more aggressive when it develops during pregnancy.

A small percentage of people with DFSP have an aggressive type called fibrosarcomatous dermatofibrosarcoma protuberans (DFSP-FS). These tumors are more likely to spread and come back after surgical removal.

DFSP is a rare cancer that affects approximately 4 out of 1 million people worldwide each year. They account for 1% to 6% of all soft tissue sarcomas.

The cancer typically affects adults ages 20 to 50, but children also get this skin cancer. Some infants have DFSP at birth. DFSP appears to affect people who are Black more often than people of other ethnicities.

**Types of DFSP**

Pathologists (doctors who examine bodies and body tissues) examine cells under a microscope to determine the type of DFSP. Types include:

* **Bednar tumors (pigmented DFSP)** contain cells that have a lot of melanin, the substance that gives skin its color. Bednar tumors may have a mix of colors, including red, brown, blue and purple. These tumors account for about 5% of DFSP diagnoses.
* **Giant cell fibroblastoma** consists of giant cells. This type is also known as juvenile DFSP because it mostly affects children and teens.
* **Fibrosarcomatous dermatofibrosarcoma protuberans (DFSP-FS)** is a more aggressive cancerous soft tissue sarcoma.
* **Myxoid DFSPs** are made of an abnormal type of connective tissue called myxoid stroma. This type of DFSP is rare.

**Symptoms and Causes**

As many as 9 in 10 people who develop DFSP have a gene change (mutation) that causes the condition. This gene change occurs in cells after you’re born. You don’t inherit a gene mutation from a parent that causes DFSP.

**Risk factors for DFSP**

In addition to racial factors, a skin injury or scars may increase your risk of DFSP. Causes of skin injuries include:

* Burns.
* Radiation therapy.
* Surgical incisions.
* Tattoos.

**What are the signs of DFSP?**

Early symptoms of DFSP are easy to dismiss or not notice. The tumors typically appear on your chest, back, shoulders, abdomen or buttocks. Tumors can also form on your arms, legs, scalp and inside of your mouth.

At first, you may notice a small patch of skin that looks like a bruise. The spot is flat and painless. It may feel rough and look discolored.

In infants and children, DFSP can look like a birthmark. These spots are usually about 1/2 inch to 2 inches (1 centimeter to 5 centimeters) across.

DFSP symptoms become more noticeable as the cancer grows. The growing tumor pushes into the top layer of skin (epidermis). Firm lumps (nodules) of tissue appear on the skin (“protuberans”).

You may notice that the nodules are:

* Easy to crack open or bleed.
* Firmly attached to your skin (don’t move).
* Getting bigger and stretching your skin.
* Hard or rubbery.
* Reddish-brown to violet, blue or red.
* Tender.

**What other conditions cause DFSP symptoms?**

A noncancerous skin condition called cellular dermatofibroma can look like DFSP, especially during the cancer’s early stage. Cellular dermatofibromas are benign soft tissue tumors that typically appear on your legs. They may be itchy or painful. Most dermatofibromas don’t need treatment.

**Diagnosis and Tests**

Dermatologists, medical doctors who specialize in skin cancer and skin diseases, diagnose DFSP. Your provider will perform a skin biopsy to remove part or all of the growth. Pathologists examine the tissue under a microscope to check for cancer cells.

If the skin biopsy determines you have DFSP, you may get an MRI to determine the size and depth of the tumor.

**Management and Treatment**

Surgical removal is the treatment of choice for DFSP. Dermatologists perform Mohs surgery to remove DFSP tumors. During the procedure, your provider:

* Injects a local anesthetic into the treatment area to numb it.
* Surgically cuts out (excises) the cancerous tumor, including a small amount of surrounding healthy tissue (called the margin).
* Uses a microscope to examine the tissue edges (margin) for cancer cells.
* Removes more tissue from the tumor site, if cancer cells are seen at the margins.
* Stops removing tissue when they can’t find any more cancer cells in the margin.
* Performs reconstructive surgery.

**Nonsurgical DFSP treatments**

DFSP tumors can grow back after surgical removal. 20% to 30% or more of people experience a recurrence of DFSP within three years after wide excision, and up to 4% to 5% recur after Mohs surgery. But tumors can recur for 10 years or more.

Healthcare providers use imatinib to treat metastatic DFSP or tumors that are too large or difficult to surgically remove. Imatinib can also shrink the tumor, making surgical removal possible. Radiation treatment can be done for incompletely excised DFSP or inoperable DFSP.

**Dermatofibrosarcoma Protuberans (DFSP) Treatment Drugs and Their Side Effects**

## Key Drug: Imatinib Mesylate (Gleevec)

* Mechanism:  
  Imatinib is a targeted therapy that inhibits the platelet-derived growth factor receptor (PDGFR) tyrosine kinase. Over 90% of DFSP tumors have a characteristic chromosomal translocation t(17;22) that leads to constitutive activation of PDGFR, driving tumor growth. Imatinib blocks this signaling, causing tumor cell death or shrinkage.
* Indications:  
  Imatinib is FDA-approved for adult patients with DFSP that is:
  + Unresectable (cannot be removed surgically),
  + Recurrent after surgery,
  + Metastatic (spread to other parts of the body).
* Clinical Use:  
  Imatinib can be used as:
  + Neoadjuvant therapy to shrink tumors before surgery, potentially enabling less extensive surgery,
  + Treatment for advanced or metastatic disease when surgery is not an option.
* Typical Dosage:  
  Usually 400 mg once or twice daily, adjusted based on tolerance and response.

## Side Effects of Imatinib

| **Side Effect Category** | **Common Symptoms** |
| --- | --- |
| Gastrointestinal | Nausea, vomiting, diarrhea, abdominal pain |
| Hematologic | Low blood counts (anemia, neutropenia, thrombocytopenia) |
| Musculoskeletal | Muscle cramps, joint pain |
| Fatigue | General tiredness and weakness |
| Skin reactions | Rash, edema (swelling), fluid retention |
| Liver effects | Elevated liver enzymes (monitoring required) |
| Other | Headache, dizziness, mild fluid retention, rarely cardiac toxicity |

* Most side effects are manageable with supportive care and dose adjustments.

## Other Treatment Options for DFSP

* Surgery:  
  The primary and most effective treatment is complete surgical excision with wide margins or Mohs micrographic surgery to minimize local recurrence.
* Radiation Therapy:  
  Sometimes used for unresectable tumors or when surgical margins are positive and further surgery is not feasible

**Outlook / Prognosis**

With proper treatment, more than 99% of people with this nonaggressive, slow-growing cancer live 10 years or longer.

**What steps can I take to improve my outlook?**

These steps may improve your outlook:

* Regularly perform skin self-exams to detect skin changes early.
* Get skin exams at your provider’s office every three to six months for the first three years after treatment (and then annually) or as recommended by your provider.
* Minimize sun exposure (which increases your risk for other skin cancers) by applying sunscreen, wearing sun-protective clothing and avoiding the outdoors when the sun’s ultraviolet (UV) rays are strongest.

**When should I call my provider?**

You should call your healthcare provider if you notice new skin changes, such as:

* Persistent bumps or growths or new skin growths.
* Changes to moles, birthmarks, scars or tattoos.
* Skin growths that bleed easily.

## 

## **Differential Diagnoses**

* Cellular fibrous histiocytoma
* Solitary fibrous tumor
* Spindle cell lipoma
* Angiosarcoma
* Peripheral nerve sheath tumors
* Spindle cell melanoma
* Angiomyxoma
* Myxoid sarcoma
* Synovial sarcoma
* Sarcomatoid carcinoma
* Cutaneous melanoma
* Dermatofibroma
* Dermatologic metastatic carcinoma
* Epidermal inclusion cyst
* Keloid
* Morphea

## **Epidemiology**

### Frequency

*United States*

Dermatofibrosarcoma protuberans (DFSP) accounts for less than 0.1% of all malignant neoplasms and approximately 1% of all soft tissue sarcomas. DFSP is the most common type of cutaneous sarcoma. The incidence of DFSP has been estimated to be 0.8-5 cases per million population per year in 2 separate studies.In another study based on data from 9 cancer registries from 1973-2002, the annual incidence of DFSP in the United States was 4.2 cases per million population per year.

*International*

The annual incidence of DFSP is reported as 3 cases per million population from a population-based cancer registry from 1982-2002 in France.A study of the Swedish population-based National Cancer Registry from 1990-2005 showed that the incidence of DFSP was approximately 4 cases per million per year.

### Race

DFSP has been reported in persons of all races, and no racial predilection seems to exist in previous reports. However, a study conducted by Criscione and Weinstock found the incidence among African Americans (6.5 cases per million population) was almost double the incidence among US Whites (3.9 cases per million population).

An uncommon pigmented variant of DFSP, accounting for 1% of all DFSP cases, is called the Bednar tumor. Annual incidence of Bednar tumor among Blacks is 7.5 times higher than that in White patients.Note the images below.

### Sex

Several studies of DFSP reveal an almost equal sexual distribution or a slight male predominance. In a large study of 902 patients with DFSP conducted by Rutgers et al, 514 (57%) patients were male and 388 (43%) patients were female.A study based on 405 DFSP cases from the Swedish National Cancer Registry between 1990 and 2005 found a very small difference in annual incidence in males versus females: 4.4 versus 4.0 cases per million, respectively.However, in Criscione and Weinstock's US cancer registry study of 2885 cases, the annual incidence of DFSP was slightly higher in females, at 4.4 cases per million versus 4.2 cases per million in males.

### 64Age

DFSP can occur at any age, but is most frequent in adults aged 20-50 years. Rarely, DFSP has been reported in newborns and elderly individuals (80 y)

**DFSP Treatment Drug Information and Their Side Effects**

The primary drug used in the treatment of Dermatofibrosarcoma Protuberans (DFSP), especially for unresectable, recurrent, or metastatic cases, is Imatinib mesylate (Gleevec).

## Imatinib (Gleevec)

* Mechanism:  
  Imatinib is a tyrosine kinase inhibitor targeting the PDGFB receptor, which is abnormally activated in DFSP due to a characteristic fusion gene (COL1A1-PDGFB). This blocks tumor growth signals.
* Indications:  
  Used for DFSP that cannot be fully removed by surgery or has recurred or spread.
* Dosage:  
  Typically 400 mg once or twice daily, adjusted based on response and tolerance.

## Common Side Effects of Imatinib

| **Side Effect Category** | **Description & Frequency** |
| --- | --- |
| Gastrointestinal | Nausea, vomiting, diarrhea, abdominal pain, upset stomach, acid reflux |
| Fluid retention | Edema/swelling, especially in legs, ankles, feet, and around eyes (very common, ~60%) |
| Fatigue | Tiredness and weakness (common, ~39%) |
| Musculoskeletal | Muscle cramps, muscle pain, joint pain, stiffness |
| Skin reactions | Rash, itching, blistering, peeling, redness |
| Hematologic | Low blood counts (anemia, neutropenia, thrombocytopenia) |
| Respiratory | Cough, upper respiratory infections, shortness of breath (common) |
| Neurologic/Psychiatric | Headache, dizziness, insomnia, depression, anxiety (some reported) |
| Liver effects | Elevated liver enzymes; rare cases of liver damage (monitoring required) |
| Serious but rare | Gastrointestinal bleeding (black/tarry stools, vomiting blood), heart issues, pulmonary complications |

Most side effects appear early and may improve over time or with dose adjustment. Serious side effects require prompt medical attention.

## Additional Considerations

* Drug interactions: Imatinib interacts with many drugs (e.g., antifungals, antibiotics, St. John's Wort) that may increase or decrease its blood levels, affecting efficacy and toxicity.
* Pregnancy & breastfeeding: Imatinib is harmful to a fetus and is excreted in breast milk; avoid use in pregnancy and breastfeeding.
* Monitoring: Regular blood tests to monitor blood counts, liver function, and side effects are essential.

**Genomic Data on Dermatofibrosarcoma Protuberans (DFSP)**

* The hallmark genomic alteration in DFSP is a somatic chromosomal translocation t(17;22)(q22;q13), which fuses part of the COL1A1 gene (chromosome 17) with part of the PDGFB gene (chromosome 22). This fusion gene produces an abnormal protein that constitutively activates the PDGFB receptor, driving uncontrolled cell proliferation and tumor formation.
* This COL1A1-PDGFB fusion gene is present in over 90% of DFSP cases, making it a highly specific diagnostic marker and therapeutic target.
* Beyond this classic fusion, whole-genome sequencing studies have revealed additional genomic complexity:
  + Novel mutations in genes such as MUC4, MUC6, KMT2C, and BRCA1 have been identified, leading to the classification of three molecular subtypes of DFSP based on MUC4 and MUC6 mutations.
  + Structural aberrations including genomic rearrangements on chromosomes 17q and 22q cause oncogene amplifications (e.g., AKT1, SPHK1, COL1A1, PDGFB) and tumor suppressor deletions (e.g., CDKN2A/B).
  + A novel gene fusion, SLC2A5-BTBD7 [t(1;14)], was also discovered, representing a potential new diagnostic and therapeutic target.
* The genomic alterations affect key pathways involved in DNA repair, cell cycle regulation, phosphoinositide 3-kinase (PI3K), and Janus kinase (JAK) signaling, contributing to tumor development and progression.
* In cases of imatinib resistance, additional somatic mutations have been identified in genes such as ACAP2, CARD10, KIAA0556, PAAQR7, PPP1R39, SAFB2, STARD9, and ZFYVE9, highlighting the molecular mechanisms behind treatment failure and the need for personalized therapy approaches.
* DFSP is generally a sporadic, non-inherited tumor, with these genetic changes arising as somatic mutations during the patient’s lifetime rather than being passed down geneticall

**Doctor-patient conversation about Dermatofibrosarcoma Protuberans (DFSP)**

Doctor: Good morning, thank you for coming in today. I want to discuss the results of your biopsy and what it means.

Patient: Thanks, doctor. I’m a bit nervous. What did the biopsy show?

Doctor: The biopsy confirmed you have a rare type of skin cancer called Dermatofibrosarcoma Protuberans, or DFSP for short. It’s a slow-growing tumor that starts in the middle layer of your skin.

Patient: Cancer? That sounds serious. Is it aggressive? Has it spread?

Doctor: DFSP tends to grow slowly and rarely spreads to other parts of the body. It usually stays localized to the skin and underlying tissue. That said, it can grow quite large if untreated, and it has a tendency to come back in the same area if not completely removed.

Patient: What are my treatment options?

Doctor: The main treatment is surgical removal, ideally using a technique called Mohs surgery. This surgery removes the tumor layer by layer, checking each layer under the microscope until no cancer cells remain. This helps preserve as much healthy tissue as possible and lowers the chance of recurrence.

Patient: What if the tumor is too big or in a tricky spot?

Doctor: In cases where surgery is difficult or the tumor is very large, we can use a targeted drug called imatinib. This medication blocks the abnormal signals that cause the tumor to grow and can shrink the tumor, making surgery easier or sometimes controlling the tumor if surgery isn’t an option.

Patient: Are there other treatments?

Doctor: Radiation therapy is sometimes used if the tumor can’t be fully removed or if surgery isn’t possible. But surgery remains the cornerstone of treatment.

Patient: What about side effects from the drug or radiation?

Doctor: Imatinib can cause side effects like nausea, fatigue, swelling, muscle cramps, and skin rash, but many patients tolerate it well. Radiation can cause skin irritation and fatigue. We will monitor you closely and manage any side effects that arise.

Patient: What are the chances of cure?

Doctor: With proper treatment, more than 99% of people with DFSP live 10 years or longer. However, because the tumor can recur locally, we’ll need to follow you regularly for several years after treatment.

Patient: What should I watch for after treatment?

Doctor: It’s important to check the area where the tumor was removed for any new lumps or changes. If you notice anything unusual, contact us promptly. We’ll also schedule regular follow-ups every 6 to 12 months.

Patient: Thank you, doctor. That helps me understand what to expect.

Doctor: You’re welcome. We’ll work together every step of the way. I’ll have my nurse provide you with some written information and support resources as well.

**What should I ask my provider?**

You may want to ask your healthcare provider:

## **What caused the skin cancer?**

* The exact cause of DFSP is not fully understood.
* It is linked to a genetic mutation that occurs in skin cells after birth, specifically a chromosomal translocation between chromosomes 17 and 22, creating a fusion gene called COL1A1-PDGFB that drives tumor growth.
* Risk factors include:
  + Age (most often diagnosed between 20 and 50 years)
  + Race (more common in Black people)
  + Prior skin injuries such as burns, scars from surgery, radiation exposure, or tattoos
* About 10% of patients report a history of trauma or skin injury at the tumor site, but this is not definitive.

## 2. **Am I at risk for other types of skin cancer?**

* DFSP itself is a rare and distinct tumor, and having DFSP does not necessarily increase your risk for other skin cancers like melanoma or basal cell carcinoma.
* However, if you have had prior radiation or significant skin damage, that may increase your general skin cancer risk.
* It’s important to maintain regular skin checks and protect your skin from UV damage.

## 3. **What’s the best treatment for me?**

* The best treatment for DFSP is complete surgical removal, ideally with Mohs micrographic surgery or wide local excision with clear margins to reduce recurrence risk.
* If the tumor is large, in a difficult location, or cannot be completely removed, targeted therapy with imatinib (a drug that blocks the abnormal fusion protein) may be recommended to shrink the tumor or control disease.
* Radiation therapy is an option if surgery is not feasible or margins are positive.
* Your treatment plan will be personalized based on tumor size, location, and other health factors.

## 4. **Am I at risk for metastatic cancer?**

* DFSP is usually a slow-growing tumor that rarely spreads (metastasizes) to other parts of the body.
* Metastasis occurs in less than 5% of cases, typically after multiple recurrences or in very advanced disease.
* The main concern is local recurrence at the original site if the tumor is not completely removed.

## 5. How often should I get cancer screenings?

* After treatment, regular follow-up exams are essential to monitor for recurrence.
* Typically, follow-ups are recommended every 6 to 12 months for at least 5 years, sometimes longer.
* During follow-up visits, your doctor will examine the treated area and may order imaging if there is suspicion of recurrence.
* You should also perform self-examinations and report any new lumps, skin changes, or symptoms promptly.

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**OLIGODENDROGLIOMA**

**DEFINITION AND DESCRIPTION**

Oligodendroglioma is a type of brain tumor, but in rare cases, it can form in your spinal cord. These tumors develop from a specific type of glial cell: oligodendrocytes. Glial cells are the support cells of your nervous system. They maintain and protect the neurons that send and relay signals within, to and from your brain.

Tumors that come from glial cells are called gliomas. Oligodendrogliomas account for between 5% and 15% of all gliomas, and about 3% to 4% of all brain tumors. Worldwide, healthcare providers diagnose just under 24,000 people with oligodendroglioma each year. Most people who have it are between the ages of 40 and 50.

**Oligodendrocytes**

The name “oligodendrocyte” comes from several Greek words and breaks down like so:

* Oligo-: Small.
* -dendro-: Tree-like.
* -cytes: Cells.

Every neuron has a main cell body with an arm-like extension called an axon. Many neurons have a myelin sheath around their axon. This fatty coating protects the axon and maintains signal speed as it passes through the neuron.

Oligodendrocytes have a main body and dozens of arm-like extensions that wrap around the axons of about 30 to 40 nearby neurons (which is why oligodendrocytes are “tree-like”). These extensions provide the myelin sheath for the axons of the connected neurons.

**Types of oligodendrogliomas**

The World Health Organization (WHO) grading scale ranges from grade 1 (lowest) to grade 4 (highest). Oligodendrogliomas fall into two main types under this grading scale:

* **Oligodendrogliomas WHO grade 2**: Also known as “low-grade oligodendrogliomas,” these oligodendrogliomas typically grow slowly. They also tend to respond well to treatment.
* **Oligodendrogliomas WHO grade 3**: Also known as “high-grade oligodendrogliomas” (and formerly known as “anaplastic oligodendrogliomas”), these are malignant. That’s because they’re more aggressive. They may spread faster and be harder to treat.

**Symptoms and Causes**

Like many brain cancers, oligodendrogliomas often don’t cause symptoms until they disturb brain tissue around them. The most common symptoms are headaches or seizures. Up to 80% of people with oligodendroglioma will have a seizure because of this cancer. That’s because oligodendrogliomas commonly affect your cerebral cortex, the wrinkled outer surface of your brain. The cortex is home to brain areas that control many of the abilities you use in everyday life, like vision, language, muscle control and more.

Besides seizures, oligodendrogliomas may cause focal symptoms. These symptoms indicate a problem that’s focused (hence the name “focal”) in a specific area of your brain. They usually affect a body part or an ability. Examples of focal symptoms can include:

* Muscle weakness or paralysis, especially on one side of your body or face.
* Hearing loss.
* Trouble speaking or understanding others who are talking (aphasia).
* Vision loss, double vision or blurred vision.
* Memory problems.
* Trouble thinking or concentrating.

**What causes oligodendroglioma?**

By definition, all oligodendrogliomas happen because of two specific DNA changes:

* **1p/19q co-deletion**: Chromosomes are the compressed DNA “data” your cells use as an instruction manual. Sometimes, errors happen when chromosomes are copied as your cells reproduce. Oligodendrogliomas always have deletions on the short (p) arm of chromosome 1 and the long (q) arm of chromosome 19. Experts often refer to this as a “1p/19q co-deletion.”
* ***IDH1 or IDH2*** **mutation**: Genes are sections of the data in your DNA that contain specific instructions. One of these tells your body how to make an enzyme called isocitrate dehydrogenase (IDH), which helps with certain types of metabolism. Two IDH mutations, *IDH1* or *IDH2*, can cause oligodendrogliomas.

The above genetic changes are all “de novo,” which means “new.” That means these mutations and deletions happen spontaneously. You don’t inherit them from either of your biological parents.

**Risk factors for oligodendroglioma**

Researchers haven’t confirmed any risk factors for oligodendroglioma. But there’s research that could mean past radiation therapy (like the type used to treat other cancers) is a possible factor for developing similar tumors called gliomas. More research is necessary to confirm if that could be a cause or contributing factor.

**Complications of oligodendroglioma**

Oligodendrogliomas affect your brain, so they can cause many possible complications. The complications you could experience depend on many factors, especially the location of the oligodendroglioma, other health conditions you have and more.

Some complications to be aware of include:

* **Malignant transformation**: Low-grade oligodendrogliomas that aren’t cancer can sometimes “transform.” That means the cells in the tumor change over time and become cancerous.
* **Strokes or similar circulatory-related problems**: Oligodendroglioma growing inside your skull or brain will take up more and more space, displacing the brain tissue around it. That can lead to strokes or stroke-like events.
* **Skull structure changes**: Oligodendrogliomas are often calcified, meaning they harden because calcium accumulates in them. When that happens on the outside of your brain, it can start to affect the bone of your skull. Slow-growing oligodendroglioma may cause surrounding bone tissue to shift or change, too.

**Diagnosis and Tests**

A healthcare provider will diagnose oligodendroglioma using multiple methods, including:

* A physical and neurological exam.
* Diagnostic imaging.
* A brain biopsy and pathology testing.

Diagnostic imaging is especially important with oligodendrogliomas because it lets providers “see” inside your head. The scans that are most likely to help are:

* **Computed tomography (CT) scans**: These are often the first imaging scan after a person has a seizure or any focal symptoms. Your bones contain calcium, so they’re bright on X-rays and CT scans. Oligodendrogliomas also often contain calcium, so they also often show up brightly.
* **Magnetic resonance imaging (MRI) scans**: These scans can clearly display the different structures inside your head. They can help determine the size of an oligodendroglioma and its precise location.

But imaging scans alone aren’t enough to diagnose an oligodendroglioma. They only provide evidence that you have a tumor in your brain that might be an oligodendroglioma. That evidence is what providers use to determine if you need a brain biopsy and pathology testing.

A brain biopsy is a surgical procedure where a neurosurgeon will collect a tiny tumor sample. The tumor sample then goes to a lab for analysis. The analysis will look at the cells under a microscope for visible changes. The sample will also undergo genetic/molecular testing to determine if you have a 1p/19q chromosome co-deletion and an IDH mutation. If testing finds both, a healthcare provider can diagnose the tumor as an oligodendroglioma.

Depending on your symptoms, medical history and any other health concerns, there are other tests you might need to undergo. Your healthcare provider can recommend these tests and explain why they may help.

**Management and Treatment**

Oligodendrogliomas are among the more treatable brain tumors and cancers. The treatment often involves multiple methods, including:

* Surgery.
* Chemotherapy.
* Radiation therapy.

**Surgery**

Brain surgery aims to remove as much of the tumor as possible. Sometimes, a neurosurgeon can remove the whole tumor. The success rate of surgery depends strongly on the type of oligodendroglioma, how much it’s progressed, the tumor’s location, your surgeon’s expertise and other factors.

Depending on surgery outcomes, the amount of tumor your surgeon is able to remove, the tumor grade, your age and your general health, you may or may not need radiation therapy and/or chemotherapy. Your care team will explain all the options for you based on the National Comprehensive Cancer Network (NCCN) guidelines.

**Chemotherapy**

Certain chemotherapy drugs are very effective against oligodendroglioma. The most likely chemotherapy treatments are:

* **The PCV regimen**: The name of this regimen comes from the three drugs it consists of: procarbazine, lomustine (often known by its chemical abbreviation “CCNU,” making it the “C” in PCV) and vincristine. PCV is generally the first option for treating oligodendroglioma.
* **Temozolomide**: Healthcare providers sometimes recommend this drug instead of the PCV regimen. The side effects of temozolomide are usually not as severe as those possible with the PCV regimen, and research shows its effectiveness is very similar to PCV.

**Radiation therapy**

Radiation therapy is very common with oligodendroglioma. This approach bombards tumor cells with enough energy to destroy them. The radiation is targeted as precisely as possible. The goal is to destroy as much of a tumor as possible while leaving surrounding healthy tissue unharmed.

**Complications/side effects of the treatment**

The side effects or complications of oligodendroglioma treatments depend strongly on the treatments themselves and other factors. Your healthcare provider is the best person to tell you more about the side effects or complications that are most likely in your case and what you can do about them.

**Outlook / Prognosis**

Oligodendroglioma is a type of brain tumor, so it’s a serious concern. But it’s more treatable and less dangerous than other types of gliomas.

Most people won’t know they have oligodendroglioma until they have symptoms, especially seizures or headaches. A first-time seizure is always something that needs emergency medical care. Headaches need medical attention when they’re frequent, happen with certain activities or occur in a way that disrupts your life.

Having symptoms is usually what leads to an imaging test that first detects an oligodendroglioma. Once detected, a healthcare provider will recommend testing to diagnose what you have and determine how to treat it. Treating oligodendroglioma is important because even low-grade, benign tumors can eventually turn into cancer. Limiting the spread of oligodendroglioma is a key way to prevent further complications or spreading to other parts of your body.

**What’s the outlook for oligodendroglioma?**

An oligodendroglioma is serious, but the outlook tends to be positive. The five-year survival rates (the percentage of people who are alive five years after diagnosis) for low-grade oligodendrogliomas range from 69% to 90%. Younger adults have a higher five-year survival rate. The five-year survival rates for high-grade oligodendroglioma are 45% to 76%.

There’s also a new drug that researchers are working on that shows promise for oligodendrogliomas with IDH mutations. This drug is still in development, but the early data indicates that it could increase the odds of a better outcome.

**Prevention**

Experts don’t know why oligodendrogliomas happen or what makes them more likely to occur. Because of that, there’s no way to prevent it or reduce your risk of having it.

**Living With**

If you have oligodendroglioma, your healthcare provider will help you decide which treatment approach is best for you. They’ll also recommend a treatment schedule and regular follow-up visits.

Going to your treatments and follow-up visits is very important. Receiving treatment consistently and as recommended is also vital.

Side effects are common with many of the treatments for oligodendroglioma. Your healthcare provider can help you understand the possible side effects that are most likely to affect you and what you can do about them.

**DIFFERENTIAL DIAGNOSIS**

Diffuse astrocytoma is the primary differential diagnosis on imaging and is virtually indistinguishable from OG. On imaging studies, diffuse astrocytoma often has less dystrophic calcification and more white matter and less cortical involvement than the OG. However, the main discriminating factors between the 2 tumor types are the genetic markers, where the lack of the 1p/19q deletion occurs in the astrocytoma.

Glioblastoma is an important diagnostic consideration from OG because this tumor carries a much poorer prognosis and is, unfortunately, much more common in adults than children. Glioblastoma will typically demonstrate more avid and heterogeneous enhancement than low-grade OG. Although glioblastoma may be hard to distinguish from the higher grade, it enhances anaplastic OG. Glioblastoma can sometimes have patchy areas of restricted diffusion and areas of central necrosis, which are both uncommon in OG. Calcification is uncommon in glioblastoma and very common in OG. Histologically, glioblastoma will have more aggressive features such as necrosis and neovascularization, and they lack the 1p/19q deletion and are often IDH mutation negative compared to OG on molecular analysis.

Dysembryoplastic neuroepithelial tumors (DNETs) are another low-grade cortical-subcortical-based neoplasm that can look similar to OG in imaging studies. However, DNETs tend to have a more “bubbly” cystic T2 hyperintense appearance and may have adjacent cortical dysplasia. Compared to OGs, which are more often diagnosed in older adults, DNETs are more often found in children and young adults. Ganglioglioma is another cortical-subcortical neoplasm that occurs more often in children and young adults and can be a seizure focus. On MRI, gangliogliomas typically present as cysts with enhancing nodules and are more commonly seen in the temporal lobe than the OG. A multinodular and vacuolating neuronal tumor is a cortical-subcortical lesion that may have imaging overlap with OG and typically appears as a cluster of small bubbly cysts that are T2/FLAIR hyperintense and do not typically enhance. The lesion is typically incidentally found and maybe a malformation/dysplastic lesion instead of a true neoplasm.

**EPIDEMIOLOGY**

OGs are uncommon, with an incidence of 0.2 per 100,000 people, and are the third most common primary brain neoplasm following the glioblastoma and the diffuse astrocytoma. OGs comprise approximately 5% of all primary CNS tumors. These tumors have a slight male predominance, reported from 1.1 to 2, with as low as a 0.92 male-to-female ratio, as seen from the results of a study. OGs have a slight bimodal distribution but are primarily adult neoplasm, with a peak incidence occurring in the fourth and fifth decades and a smaller tumor incidence peak in children aged 6 to 12. OGs in pediatric patients usually demonstrate different molecular markers than are seen in the adult form, raising the issue of whether they represent the same neoplasm.

**Genomic Data of Oligodendroglioma**:

## Key Genomic Features

* 1p/19q Codeletion:  
  The hallmark of oligodendroglioma is the combined whole-arm deletion of chromosome 1p (short arm of chromosome 1) and 19q (long arm of chromosome 19). This 1p/19q codeletion occurs in approximately 60% of oligodendrogliomas and is a defining molecular signature distinguishing it from other gliomas.  
  This genetic alteration is strongly associated with better prognosis and increased sensitivity to chemotherapy and radiation.
* IDH1 or IDH2 Mutation:  
  Almost all oligodendrogliomas harbor mutations in the isocitrate dehydrogenase genes (IDH1 or IDH2). The presence of an IDH mutation together with 1p/19q codeletion is required for a definitive diagnosis of oligodendroglioma according to WHO classification.  
  IDH mutations are early events in tumorigenesis and correlate with improved survival.
* TERT Promoter Mutation:  
  The TERT promoter mutation is present in the majority of oligodendrogliomas and is involved in telomerase activation, contributing to tumor cell immortality. This mutation often co-occurs with 1p/19q codeletion and IDH mutation.
* Other Recurrent Mutations:
  + CIC mutations occur in about 70% of cases. CIC is a tumor suppressor gene, and its mutation contributes to tumor development.
  + FUBP1 mutations are found in 20–30% of tumors and also play a role in oncogenesis.
  + NOTCH1 mutations occur in approximately 15% of cases and may influence tumor progression.
* Absence of ATRX and TP53 Mutations:  
  Unlike astrocytomas, oligodendrogliomas typically lack ATRX and TP53 mutations, which helps in differential diagnosis.
* Methylation Profile:  
  DNA methylation profiling supports the diagnosis and classification of oligodendrogliomas and correlates with molecular alterations

## **Doctor-Patient Conversation: Oligodendroglioma**

Doctor: Good afternoon, Mr. Smith. I have your test results here, and I’d like to discuss them with you. How are you feeling today?

Patient: Hello, Doctor. I’m a bit anxious, to be honest. I’ve been worried since the MRI.

Doctor: That’s completely understandable. Let me explain what we found. Your MRI and biopsy show that you have a type of brain tumor called oligodendroglioma. It’s a tumor that arises from cells called oligodendrocytes, which support nerve cells in the brain.

Patient: Is it cancer? How serious is it?

Doctor: Yes, it is a type of brain cancer, but it tends to grow more slowly than some other brain tumors. It’s classified as a glioma, and based on the pathology and genetic testing, your tumor has some features that are actually associated with a better prognosis than other brain tumors.

Patient: What kind of features?

Doctor: Your tumor has mutations in the IDH gene and a genetic change called 1p/19q codeletion. These are markers that we look for because they tell us your tumor is more likely to respond well to treatment and that the overall outlook is better.

Patient: That’s a relief. What treatments will I need?

Doctor: The first step is usually surgery to remove as much of the tumor as safely possible. This helps reduce pressure on your brain and gives us tissue to analyze. After surgery, we typically recommend radiation therapy combined with chemotherapy to target any remaining tumor cells.

Patient: What kind of chemotherapy?

Doctor: The standard chemotherapy for oligodendroglioma is a combination called PCV, which includes procarbazine, lomustine, and vincristine. Another option is temozolomide, which is often better tolerated. We’ll discuss which is best for you based on your overall health.

Patient: What are the side effects of these treatments?

Doctor: Surgery risks depend on the tumor location but can include temporary or permanent neurological changes. Radiation can cause fatigue, skin irritation, and sometimes memory or cognitive changes. Chemotherapy side effects vary: PCV can cause nausea, low blood counts, and nerve symptoms, while temozolomide usually causes milder nausea and fatigue. We’ll monitor you closely and provide support to manage these effects.

Patient: How long will treatment take? What’s my outlook?

Doctor: Treatment usually spans several months, starting with surgery, then radiation and chemotherapy over the following weeks to months. With your tumor’s genetic profile and treatment, many patients live for many years with good quality of life. We’ll also schedule regular follow-ups with MRI scans to monitor for any changes.

Patient: That sounds like a plan. Is there anything I can do to improve my chances?

Doctor: Maintaining a healthy lifestyle, managing stress, and adhering to follow-up appointments are important. Also, avoid smoking and excessive alcohol. We have support services to help you through treatment.

Patient: Thank you, Doctor. I feel better knowing what to expect.

Doctor: You’re welcome. We’re here to support you every step of the way. Please don’t hesitate to ask any questions as they come up.

**What questions should I ask my doctor?**

You may want to ask your healthcare provider any of the following:

**Is oligodendroglioma cancer curable?**

Oligodendrogliomas are treatable, but not technically “curable,” tumors. The most likely approach to treating oligodendroglioma is to remove the whole tumor (or as much of it as possible) and then your care team determines if chemotherapy, radiation therapy or a combination of these are necessary to eradicate any remaining cancer cells.

**Is oligodendroglioma fatal?**

Like all tumors or cancers, oligodendroglioma can be fatal. But oligodendroglioma generally has higher survival rates than other gliomas and brain cancers. The chances of prolonged survival are higher with lower-grade tumors. Other factors can also play a role, so your healthcare provider can tell you more about the outlook for your specific case.

## **What grade is my oligodendroglioma?**

* Oligodendrogliomas are classified into two main grades:
  + Grade 2 (Low-grade): Slow-growing tumors with fewer abnormal cells and better prognosis.
  + Grade 3 (Anaplastic): More aggressive, faster-growing tumors with more abnormal cells and worse prognosis.
* Your exact grade depends on histological examination and molecular testing, but most oligodendrogliomas fall into these categories.

## **2. Where is it, and what abilities might it affect?**

* Oligodendrogliomas most commonly arise in the frontal lobes of the brain, but can also occur in temporal or parietal lobes.
* The tumor’s location determines symptoms and affected abilities:
  + Frontal lobe: Changes in behavior, personality, mood, concentration, and motor function.
  + Motor cortex: Weakness or numbness on one side of the body.
  + Temporal/parietal lobes: Speech and language difficulties.
  + Occipital lobe: Vision problems.
  + Other areas: Seizures (most common symptom), headaches, balance and coordination problems, memory issues.

## 3. **What are the treatment options?**

* Surgery: Maximal safe resection to remove as much tumor as possible.
* Radiation therapy: Often used after surgery, especially for higher-grade tumors or residual disease.
* Chemotherapy: PCV regimen (procarbazine, lomustine, vincristine) or temozolomide, often combined with radiation for grade 3 tumors or high-risk grade 2 tumors.

## 4. **Is it possible to remove all of the tumor with surgery?**

* Complete removal is often challenging because oligodendrogliomas are diffuse and infiltrative, spreading into surrounding brain tissue.
* Surgeons aim for maximal safe resection to remove as much tumor as possible without damaging critical brain areas.
* The extent of removal depends on tumor size, location, and involvement of eloquent brain regions.

## 5. **What are the possible complications or side effects of treatment?**

* Surgery: Risks include neurological deficits (weakness, speech problems), infection, bleeding, and swelling.
* Radiation: Fatigue, skin irritation, hair loss near treatment site, cognitive changes, and rare long-term effects like radiation necrosis.
* Chemotherapy: Nausea, vomiting, fatigue, lowered blood counts (infection risk), neuropathy (with PCV), and other drug-specific effects.

## 6. **Do you recommend chemotherapy, radiation therapy or both?**

* For low-grade (grade 2) tumors with complete resection and low risk, observation or radiation alone may be sufficient.
* For high-grade (grade 3) or incompletely resected tumors, combined radiation therapy plus chemotherapy (usually PCV) is recommended to improve survival.
* Temozolomide is an alternative chemotherapy option, often better tolerated.

## 7. **What’s the treatment timeline?**

* Surgery: Usually performed soon after diagnosis.
* Radiation therapy: Typically starts 2–6 weeks post-surgery, lasting about 5–6 weeks with daily treatments.
* Chemotherapy: Given concurrently or sequentially with radiation, lasting several months depending on regimen (e.g., PCV cycles every 6–8 weeks).
* Overall active treatment can span 3 to 9 months, followed by long-term monitoring.

## 8. During and after treatment, what symptoms mean I need immediate medical attention?

Seek urgent care if you experience:

* Sudden severe headache or worsening headache not relieved by medication
* New or worsening seizures or convulsions
* Sudden weakness, numbness, or paralysis on one side of the body
* Difficulty speaking, understanding speech, or sudden confusion
* Loss of vision or double vision
* Severe nausea, vomiting, or inability to keep fluids down
* Signs of infection (fever, chills, redness or swelling at surgical site)

REFERENCES

<https://www.mayoclinic.org/diseases-conditions/oligodendroglioma/symptoms-causes/syc-20576736>

<https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1425>

<https://www.ncbi.nlm.nih.gov/books/NBK559184/#article-26152.s10>

[Oligodendroglioma: Symptoms, Treatment & Prognosis](https://my.clevelandclinic.org/health/diseases/21191-oligodendroglioma#overview)

**MEDULLOBLASTOMA**

**DEFINITION AND DESCRIPTION**

Medulloblastoma (muh-dul-o-blas-TOE-muh) is a cancerous brain tumor that starts in the lower back part of the brain. This part of the brain is called the cerebellum. It is involved in muscle coordination, balance and movement.

Medulloblastoma begins as a growth of cells, which is called a tumor. The cells grow quickly and can spread to other parts of the brain. Medulloblastoma cells tend to spread through the fluid that surrounds and protects your brain and spinal cord. This is called cerebrospinal fluid. Medulloblastomas don't usually spread to other parts of the body.

Medulloblastoma can happen at any age, but most often occurs in young children. Though medulloblastoma is rare, it's the most common cancerous brain tumor in children. Medulloblastoma happens more often in families that have a history of conditions that increase the risk of cancer. These syndromes include Gorlin syndrome or Turcot syndrome.

**SYMPTOMS**

Medulloblastoma symptoms happen when the cancer grows or causes pressure to build up in the brain. Signs and symptoms of medulloblastoma may include:

* Dizziness.
* Double vision.
* Headaches.
* Nausea.
* Poor coordination.
* Tiredness.
* Unsteady walk.
* Vomiting.

**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 not clear what causes medulloblastoma. This cancer starts as a growth of cells in the brain.

Medulloblastoma happens when cells in the brain 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 grow and multiply quickly. Cancer cells can keep living when healthy cells die. This causes too many cells.

The cancer cells form a mass called a tumor that can grow to push on nearby structures. The cancer cells can invade and destroy healthy body tissue. They also can spread to other areas.

**Risk factors**

Factors that may increase the risk of medulloblastoma include:

* **Young age.** Medulloblastoma can happen at any age. This cancer happens most often in children.
* **Inherited syndromes.** Medulloblastoma happens more often in families that have a history of conditions that increase the risk of cancer. These conditions include Fanconi anemia, Gorlin syndrome, Li-Fraumeni syndrome, Rubinstein-Taybi syndrome and Turcot syndrome.

**Diagnosis**

The process of diagnosis usually starts with a medical history review and a discussion of signs and symptoms. Tests and procedures used to diagnose medulloblastoma include:

* **Neurological exam.** During this exam, vision, hearing, balance, coordination and reflexes are tested. This can help show which part of the brain might be affected by the tumor.
* **Imaging tests.** Imaging tests capture pictures of the brain. The pictures can show the size and location of the tumor. These tests may show pressure or blockages of the cerebrospinal fluid. CTs and MRIs are used for the imaging, but other tests might be needed in certain situations.
* **Tissue sample testing.** A biopsy is a procedure to remove a sample of the tumor for testing. Biopsies for medulloblastoma are uncommon but might be used in certain situations. In a biopsy, part of the skull is removed. A needle is used to take a sample of the tumor. The sample is tested in a lab to see if it's a medulloblastoma.
* **Removal of cerebrospinal fluid for testing.** A spinal tap, also called a lumbar puncture, involves inserting a needle between two bones in the lower spine. The needle draws out cerebrospinal fluid from around the spinal cord. The fluid is tested in a lab to look for tumor cells. This test is only done after managing the pressure in the brain or removing the tumor.

**Treatment**

Treatment for medulloblastoma usually includes surgery followed by radiation or chemotherapy, or both. Your healthcare team considers many factors when creating a treatment plan. These factors might include the tumor's location, how fast it's growing, whether it has spread to other parts of the brain and the results of tests on the tumor cells. Your care team also considers your age and your overall health.

Treatment options include:

* **Surgery to relieve fluid buildup in the brain.** A medulloblastoma may grow to block the flow of cerebrospinal fluid. This can cause a buildup of fluid that puts pressure on the brain. To reduce the pressure, a surgeon can create a pathway for the fluid to flow out of the brain. Sometimes this procedure can be combined with surgery to remove the tumor.
* **Surgery to remove the medulloblastoma.** The goal of surgery is to remove all of the medulloblastoma. But sometimes it's not possible to fully remove the tumor because it forms near important structures deep within the brain. Most people with medulloblastoma need more treatments after surgery to kill any cancer cells that are left.
* **Radiation therapy.** Radiation therapy uses powerful energy beams to kill cancer cells. The energy can come from X-rays, protons and other sources. During radiation therapy, a machine directs beams of energy to specific points on the body. Radiation therapy is often used after surgery.
* **Chemotherapy.** Chemotherapy uses medicines to kill cancer cells. Typically, children and adults with medulloblastoma receive these medicines as an injection into veins. Chemotherapy may be used after surgery or radiation therapy. Sometimes it's done at the same time as radiation therapy.

**Recovery time**

Length of treatment can vary from person to person. Those who undergo any type of brain surgery usually need at least four to eight weeks to recover. For chemotherapy or radiation therapy, treatment could last several weeks or several months, depending on the case. To learn more about your or your child’s estimated treatment or recovery time, talk with your healthcare provider.

**Outlook / Prognosis**

Your team of medical experts may include:

* Medical oncologists
* Neurosurgeons
* Pathologists
* Physical therapists
* Radiologists
* Radiation oncologists
* Neuropsychologists

They’ll create a personalized treatment plan according to your specific needs.

**Can you survive medulloblastoma?**

In many cases, yes. While medulloblastoma has the potential to spread throughout your entire nervous system, many people can be cured. There’s a higher chance of survival if the medulloblastoma hasn’t spread to other parts of your brain and spinal cord.

**Prognosis for medulloblastoma**

The five-year medulloblastoma survival rate is over 80%. This means that over 80% of all people diagnosed with medulloblastoma are still alive five years later. Researchers base these numbers on medulloblastoma outcomes in the past.

But keep in mind, survival rates can’t tell you what will happen in your situation. To better understand survival rates and what they mean for you, talk to your healthcare provider.

**DIFFERENTIAL DIAGNOSIS**

* Other primary brain tumors:
  + Ependymoma: Often arises from the floor of the fourth ventricle, may cause obstructive hydrocephalus.
  + Astrocytoma: Diffuse gliomas that can occur in the cerebellum or brainstem.
  + Oligodendroglioma: Typically supratentorial but can mimic symptoms.
  + Meningioma: Usually extra-axial and benign but can cause mass effect.
  + Hemangioblastoma: Vascular tumor often in cerebellum.
  + Pituitary adenoma: Usually sellar region but can cause visual symptoms.
  + Schwannoma: Usually arises from cranial nerves, distinct location.
  + Primary CNS lymphoma: Can mimic mass lesions.
  + Craniopharyngioma, pinealoma: Tumors in supratentorial midline structures.
  + Atypical teratoid/rhabdoid tumor (AT/RT): More common in young children, aggressive embryonal tumor.
  + Choroid plexus carcinoma: Rare, intraventricular tumor.
* Non-neoplastic conditions:
  + Brain abscess (bacterial, tuberculosis, toxoplasmosis, cryptococcosis, aspergillosis): Infectious lesions can mimic tumors.
  + Arteriovenous malformations (AVM) or brain aneurysms: Vascular lesions may cause similar symptoms.
  + Hydatid cyst: Parasitic cystic lesion.
  + Brain metastasis: Secondary tumors from systemic cancer.
* Other embryonal tumors:
  + Primitive neuroectodermal tumors (PNETs): Historically grouped with medulloblastoma but now distinguished molecularly.

## **Epidemiology**

Epidemiology data is changing ever since we have a better understanding of molecular and genetic behaviors of these tumors and especially after the new World Health Organization (WHO) classification from 2016. [3]

### Demographics

*Age and Sex*

Incidence of medulloblastoma is 1.5-2 cases per 100,000 population, with 350 new cases in the United States each year.

Medulloblastoma accounts for 64.3% of all embryonal tumors in pediatric patients (0–19 years old), according to the Central Brain Tumor Registry of the United States (CBTRUS). Males displayed higher incidence rate relative to females (males: 0.16 vs. females: 0.12), except in patients < 1 year-old. [2] Overall ratio tends to be 1.5:1 for males. Males also tend to have poorer prognosis. Among all age groups, the reports from CBTRUS cite the embryonal tumor group together, with a total incidence rate of 0.25 per 100,000 per year with slight male predominance (0.29 vs. 0.2). Incidence of medulloblastoma decreases with age. Incidence was 0.55 per 100,000 population, 0.57 per 100,000 population, 0.32 per 100,000 population, and 0.16 per 100,000 population in children aged 0–4, 5–9, and 10–14 years, and adolescents aged 15–19 years, respectively. Incidence was highest in patients aged 1–4 years at diagnosis, but patients aged 10–14 years showed increased incidence from 2000 to 2013, and when looking at all age groups the total incidence peaks at ages 9 years and below. When looking at CBTRUS and SEER databases covering roughly the same period of time (2000/2001 to 2013) adult patients (20 years of age and older) are about 28% from all medulloblastoma patients. Interestingly enough, for the adult group there was a significant rise in incidence rate between 2001 and 2009 with subsequent significant decline in the rate between 2009 and 2013.

*Race*

In the United States, when looking at race for pediatric population (0-19 years), there is Caucasian and Asian/Pacific Islander predominance. In the collection of data from CBTRUS and SEER, white race was reported in the majority of cases (more than 80%).Yet, when comparing black population to white population for the years 2001 to 2013, blacks displayed a non-significant increase in incidence and in mortality risk.

*Mortality/Morbidity*

The 5-year and 10-year survival rates among all patients are 73% and 64.7%, respectively. Patients aged 1–4 years have lower survival rates for each year post diagnosis relative to patients aged 5–9, 10–14, and 20+ years up to 5 years post diagnosis. Survival rates for males and females are similar up to 10 years post diagnosis. Black patients displayed slightly lower survival rates for each year post diagnosis compared to white patients.Yet the reader needs to take into consideration that these survival numbers are from before the adjustment by molecular subtypes. When looking at the new classification (even before changing from 4 subtypes to 5), certain unsettled issues in epidemiology can become clearer. The group of infants < 1 year of age has a much poorer prognosis. In previous works it was described that the age group of children less than 4 years old are divided mainly to SHH (more than 50%) and group 3 (~40%). Whereas SHH pathway-driven tumors usually lead to a fair survival rate of 75% in 5 years for children below 3 years of age, group 3 for the same age group is having significantly worse survival rates. This accounts for the discrepancy between the old survival rates in CBTRUS of about 48% for children < 1 year old and 62% for children between 1 and 4 years of age, and the more positive picture that sometimes can be seen in daily life.

In terms of morbidity, there are a lot of potential causes and complications for the patient diagnosed with medulloblastoma:

* [Hydrocephalus](https://emedicine.medscape.com/article/1135286-overview): The most common complication is hydrocephalus due to compression of the normal cerebrospinal fluid (CSF) pathways. Although this is a common complication, only 10-50% of patients with preoperative hydrocephalus will need a long-term ventricular shunt. Some children can be treated with an endoscopic third ventriculostomy.
* Cerebellar dysfunction: Tumor infiltration of the cerebellum usually is in the midline, leading to difficulties with ambulation and truncal ataxia. This is more common than signs attributable to the cerebellar hemisphere (eg, extremity dysmetria). Cerebellar mutism syndrome occurs in approximately one quarter of patients who underwent resection of medulloblastoma in the immediate postoperative period. Brainstem invasion of the tumor was the only risk factor identified as having a positive correlation with the development of cerebellar mutism.
* Leptomeningeal dissemination: One of the most feared complications of medulloblastoma is dissemination within the CSF. Medical and, less commonly, surgical therapy must be directed at controlling dissemination to cranial nerves and spinal cord and related structures. This dissemination of disease portends to a high-risk stratification.

## **Modified Chang Staging System**

## T: Primary Tumor

| **Stage** | **Description** |
| --- | --- |
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Tumor <3 cm in diameter, limited to midline vermis, roof of fourth ventricle, or cerebellar hemisphere |
| T2 | Tumor ≥3 cm without extension |
| T3a | Tumor >3 cm with extension into aqueduct of Sylvius or foramen of Luschka |
| T3b | Tumor >3 cm with definite spread into brainstem |
| T4 | Tumor >3 cm extending past aqueduct of Sylvius or down past foramen magnum |

## M: Metastasis

| **Stage** | **Description** |
| --- | --- |
| M0 | No evidence of gross subarachnoid or hematogenous metastasis |
| M1 | Microscopic tumor cells detected in cerebrospinal fluid (CSF) |
| M2 | Gross nodular seeding in cerebellar or cerebral subarachnoid space or ventricles |
| M3 | Gross nodular seeding in spinal subarachnoid space |
| M4 | Metastases outside the cerebrospinal axis (e.g., extraneural metastases) |

**Medulloblastoma Genomic Data**

## The Four Principal Molecular Subgroups

| **Subgroup** | **Key Genetic Features** | **Clinical/Demographic Features** | **Prognosis** |
| --- | --- | --- | --- |
| WNT | - Activation of WNT signaling pathway |  |  |

* Mutations in CTNNB1 (β-catenin)
* Chromosome 6 monosomy | - Occurs in older children and adolescents
* Tumors arise from dorsal brainstem | Best prognosis (~90%+ survival) |  
  | SHH (Sonic Hedgehog) | - Mutations in PTCH1, SMO, SUFU, GLI1, GLI2
* Activation of SHH pathway
* Subtypes: SHHα (childhood, TP53 mutations), SHHβ (infants, metastatic), SHHγ (infants, nodular), SHHδ (adults, TERT promoter mutations) | - Occurs in infants, children, adults
* Intermediate prognosis, varies by subtype |  
  | Group 3 | - Frequent MYC amplification
* Hypomethylation phenotype
* Subtypes with varying risk: 3α (infants, better outcome), 3β, 3γ (high metastasis) | - Mostly pediatric
* Often metastatic at diagnosis
* Worst prognosis among subgroups |  
  | Group 4 | - Most common subgroup (~35%)
* Less well understood molecular drivers
* Some mutations in CBFA complex, cyclic AMP pathway
* Male predominance | - Intermediate prognosis
* Variable metastatic potential |

**Medulloblastoma Treatment Drugs and Their Side Effects**

## 1. Chemotherapy Drugs

| **Drug** | **Use in Medulloblastoma** | **Common Side Effects** |
| --- | --- | --- |
| Cisplatin | Platinum-based agent used in induction and maintenance chemotherapy | Nausea, vomiting, nephrotoxicity (kidney damage), ototoxicity (hearing loss), neuropathy, myelosuppression |
| Lomustine (CCNU) | Alkylating agent, part of PCV regimen and maintenance | Bone marrow suppression, nausea, fatigue, pulmonary toxicity (rare) |
| Vincristine | Microtubule inhibitor, given weekly during chemo and radiation | Peripheral neuropathy (numbness, tingling), constipation, hair loss |
| Cyclophosphamide | Alkylating agent used in combination regimens | Myelosuppression, hemorrhagic cystitis (bladder irritation), nausea, fatigue |
| Etoposide | Topoisomerase inhibitor used in some relapse protocols | Myelosuppression, nausea, hair loss, secondary leukemia risk |
| Temozolomide | Oral alkylating agent sometimes used in relapsed or high-risk cases | Nausea, vomiting, fatigue, low blood counts |
| Bevacizumab | Anti-angiogenic monoclonal antibody used in relapsed disease | Hypertension, bleeding risk, impaired wound healing |
| Thalidomide, Celecoxib, Fenofibrate | Used in experimental or relapse protocols (e.g., MEMMAT) | Fatigue, rash, GI upset, thromboembolism (thalidomide) |

## 2. Radiation Therapy

* Craniospinal irradiation (CSI): Standard after surgery to treat residual tumor and prevent spread through cerebrospinal fluid.
* Side effects: Fatigue, skin irritation, hair loss, cognitive changes, hormonal deficiencies, risk of radiation necrosis.

## 3. Surgery

* Maximal safe resection to remove tumor mass.
* Risks include neurological deficits, infection, bleeding, posterior fossa syndrome (speech and motor difficulties).

## 4. Treatment Protocols

* Standard-risk patients: Surgery → reduced-dose CSI → chemotherapy (e.g., cisplatin, lomustine, vincristine).
* High-risk patients: Surgery → full-dose CSI → intensified chemotherapy including cyclophosphamide, carboplatin, vincristine, and others.
* Relapsed disease: Protocols like ACNS0821 (temozolomide + irinotecan ± bevacizumab) or MEMMAT regimen (multi-drug antiangiogenic approach) are used.

## 5. Side Effects

| **Treatment Modality** | **Common Side Effects** | **Serious Risks/Notes** |
| --- | --- | --- |
| Chemotherapy | Nausea, vomiting, fatigue, low blood counts, neuropathy | Kidney damage (cisplatin), hearing loss, secondary cancers |
| Radiation | Fatigue, skin changes, cognitive decline, hormonal issues | Long-term neurocognitive impairment, radiation necrosis |
| Surgery | Neurological deficits, infection, bleeding | Depends on tumor location and extent |

## **Doctor-Patient Conversation: Medulloblastoma**

Doctor: Good afternoon . I know waiting for results can be stressful, so I want to take some time to explain what we found and what the next steps are. How are you feeling today?

Patient: Thank you, Doctor. I’m quite anxious. I just want to understand what’s going on with my son.

Doctor: Absolutely, and that’s completely understandable. Your son’s MRI and biopsy show that he has a tumor called medulloblastoma, which is a type of brain tumor that arises in the cerebellum, the part of the brain that helps with balance and coordination.

Patient: Is it cancer? How serious is it?

Doctor: Yes, medulloblastoma is a malignant brain tumor, meaning it is cancerous. However, the good news is that with modern treatment, many children do very well. The tumor is aggressive but treatable with a combination of surgery, radiation, and chemotherapy.

Patient: What does treatment involve?

Doctor: First, we’ll perform surgery to remove as much of the tumor as safely possible. This helps relieve pressure on the brain and gives us tissue to analyze further. After surgery, your son will receive radiation therapy to the brain and spinal cord to target any remaining tumor cells. We’ll also use chemotherapy drugs to help kill cancer cells and reduce the chance of recurrence.

Patient: What are the side effects? Will he be able to go to school?

Doctor: Surgery carries risks like any brain operation, including temporary weakness or balance issues, but our neurosurgery team is very experienced. Radiation can cause fatigue, hair loss, and sometimes affect memory or learning, but we use techniques to minimize these effects. Chemotherapy can cause nausea, low blood counts, and increased infection risk, but we’ll support him with medications and careful monitoring.

Many children return to school and normal activities after treatment, though some may need extra support depending on how they respond.

Patient: How long will treatment take?

Doctor: Surgery is usually a one-time procedure. Radiation therapy typically lasts about 5-6 weeks with daily sessions, followed by several months of chemotherapy. Overall, active treatment may take around 6-9 months, but we’ll tailor it to your son’s needs.

Patient: What’s the outlook? Will he be cured?

Doctor: Prognosis depends on several factors, including how much tumor we can remove, whether the cancer has spread, and the tumor’s molecular subtype. Some subtypes have excellent outcomes, with survival rates over 80-90%. We’ll perform molecular testing to better understand his tumor and personalize treatment.

Patient: What should I watch for during treatment?

Doctor: Watch for signs like severe headaches, vomiting, sudden weakness, seizures, or changes in behavior or alertness. If any of these occur, seek medical attention immediately.

Patient: Thank you, Doctor. This helps me understand what to expect.

Doctor: You’re welcome. We have a multidisciplinary team including oncologists, nurses, therapists, and support staff to help your family through this. Please feel free to ask questions anytime.

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**EPENDYMOMA**

**DEFINITION AND DESCRIPTION**

An ependymoma is a tumor that forms in your brain or spinal cord. Ependymoma is pronounced eh-PEN-de-MO-ma.

Ependymomas are primary tumors. That means they form directly in your brain or spinal cord (they don’t spread there from somewhere else in your body).

They’re a type of glioma. Ependymomas are the sixth most common brain tumor in children. But they can affect adults, too.

**Are ependymomas aggressive?**

Healthcare providers grade ependymomas on a 1 to 3 scale, based on how quickly they grow. Grade 1 tumors grow the slowest and grade 3 grow fastest.

Grade 1 and 2 ependymomas are noncancerous (benign). They usually grow slowly and don’t spread (metastasize) from where they form.

Grade 3 ependymomas are cancerous (malignant). They grow more aggressively (much faster) than lower-grade tumors.

**Types of ependymomas**

In addition to grades, there are several types of ependymomas, including:

* **Subependymomas (grade 1).** These grow near the chambers in your brain (ventricles) that contain cerebrospinal fluid (CSF). They’re more common in adults than children.
* **Classic ependymomas (grade 2).** Classic ependymomas are named that because they’re the most common type. They can affect both children and adults.
* **Myxopapillary ependymomas (grade 2).** These grow in your lower spinal cord. They’re most common in adult men.
* **Anaplastic ependymomas (grade 3)**. These usually form near the base of your brain. They grow quickly and often spread to other parts of your brain. They’re the most likely to regrow after treatment (recur).

**Symptoms and Causes**

An ependymoma can cause a lot of symptoms depending on where it forms. Some of the most common symptoms include:

* Back pain
* Balance issues
* Blurry vision or other vision changes
* Dizziness
* Headaches
* Mood swings
* Muscle weakness
* Nausea & vomiting
* Neck pain
* Numbness in your arms or legs
* Seizures
* Trouble controlling your pee (urinary incontinence)

Babies and very young children can’t tell you they’re feeling pain or other symptoms. You might notice:

* A larger-than-usual head
* Sleeplessness
* Unusual irritability or fussing
* Vomiting or spitting up more than usual

**What causes ependymomas?**

Experts aren’t sure what causes ependymomas. They may happen by mistake when ependymal cells in your brain divide and replicate. Some genetic variations may cause them.

Some studies have found that people who carry the genetic variations that cause neurofibromatosis type 2 may be more likely to develop ependymomas. But experts can’t say for sure that they’re linked. They’re still studying this possible connection.

**Diagnosis and Tests**

A healthcare provider will diagnose an ependymoma with a physical exam, a neurological exam and some tests. Your provider will ask about your symptoms, and when you first noticed them.

Your provider may use some of the following tests to diagnose an ependymoma:

* Biopsy
* CT scan
* Lumbar puncture
* MRI

**Management and Treatment**

Your healthcare provider will treat an ependymoma with:

* **Surgery**. Surgery is the most common ependymoma treatment. A surgeon will remove as much of the tumor as possible.

If the entire tumor is removed during surgery, additional treatment may not be needed. If some tumor remains, the neurosurgeon may recommend another operation to try to remove the rest of the tumor. Additional treatments, such as radiation therapy, may be recommended for cancerous tumors or if all of the tumor can't be removed.

* **Radiation therapy**. Radiation therapy uses powerful X-rays to destroy tumor cells. You might need radiation before and/or after surgery.

Radiation therapy may be recommended after surgery to help prevent cancerous tumors from coming back. It also may be recommended if neurosurgeons weren't able to remove the tumor completely.

Some special types of radiation therapy help focus the radiation treatment on the tumor cells. These special types of radiation may reduce the risk of damage to nearby healthy cells. Examples include conformal radiation therapy, intensity-modulated radiation therapy and proton therapy.

* **Chemotherapy (chemo)**. Chemo is medication that kills cancer cells. You’ll usually only need chemo if the tumor has spread to other areas of your body. This is very rare with ependymomas.
* **Immunotherapy**. You’ll take medications that boost your immune system’s ability to fight cancer. Immunotherapy is a rare treatment for an ependymoma.

### **Targeted therapy**

Targeted therapy uses medicines that attack specific chemicals in the tumor cells. By blocking these chemicals, targeted treatments can cause tumor cells to die. Targeted therapy might be an option to treat an ependymoma that comes back after treatment.

**Outlook / Prognosis**

The five-year survival rate for ependymomas is nearly 85%. That means around 85% of people are still alive within five years of being diagnosed. But this number may not apply to you or your unique situation. Your providers will tell you what can expect.

There are lots of factors that can impact your survival rate, including:

* The tumor’s grade
* The tumor’s location
* Your age
* Your overall health

**Is ependymoma cancer curable?**

There’s no cure for cancer, but it’s possible to remove or destroy a grade 3 ependymoma with treatment.

Remember, there’s always a chance an ependymoma regrows (recurs), even after you’ve been declared cancer-free. That’s much more likely with grade 3 tumors. Your providers and surgeon will tell you what to expect based on your age and overall health.

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

Your provider will tell you how often you’ll need follow-up visits to monitor any changes in your body. You’ll need regular imaging tests to keep an eye on the ependymoma during treatment.

## **Diagnostic Considerations**

With intracranial (posterior fossa) ependymoma, the differential diagnosis includes the following:

* Astrocytoma
* Medulloblastoma
* Cerebral neuroblastoma
* Choroid plexus papilloma

With intracranial (supratentorial) ependymoma, the differential diagnosis includes the following:

* Central neurocytoma
* Microcystic meningioma
* Astrocytoma
* Glioblastoma multiforme

With spinal (intramedullary) ependymoma, the differential diagnosis includes the following:

* Astrocytoma
* Metastatic tumor
* Schwannoma
* Spinal (exophytic/extramedullary)
* Schwannoma
* Paraganglioma of the filum terminale

Other diagnostic considerations include the following:

* Abscess
* Encephalitis
* Arteriovenous malformations
* Cavernous malformation
* Hemorrhage

## Differential Diagnoses

* Astrocytoma
* Choroid Plexus Papilloma
* Glioblastoma
* Tumors of the Conus and Cauda Equina
* Vascular Surgery for Arteriovenous Malformations

## 

## **Epidemiology**

Ependymomas are a relatively uncommon form of CNS neoplasm, representing about 3% of CNS tumors diagnosed in the United States overall. However, ependymomas comprise approximately 17% of all spinal tumors.

Some studies have noted a slightly increased incidence of ependymoma in males vs. females. Ependymoma incidence is higher in white people than in other races.

Epidemiological characteristics vary by ependymoma subtype. Intracranial ependymomas, particularly posterior fossa ependymomas, generally present in young children with a median age at diagnosis of 2.5 years. In one large retrospective population study, 66% of spinal tumors occurred in adults over the age of 45, and 39% of all intracranial tumors occurred in children under the age of 12.

## **Doctor-Patient Conversation: Ependymoma**

Doctor: Hello I have reviewed the results of your MRI and biopsy, and I’d like to talk with you about the diagnosis and what to expect moving forward. How are you feeling today?

Patient: I’m quite worried, doctor. What did the tests show?

Doctor: The tests show that you have a tumor called an ependymoma. This is a type of tumor that arises from the ependymal cells lining the fluid-filled spaces in your brain or spinal cord. It can occur in different parts of the central nervous system, and we’ll tailor treatment based on its location and grade.

Patient: Is it cancer? What does the grade mean?

Doctor: Ependymomas can be low-grade or high-grade. Low-grade tumors (grade 1 or 2) tend to grow more slowly, while grade 3 tumors are more aggressive. We also consider molecular features that help us understand the tumor’s behavior better. The grade and location influence treatment decisions and prognosis.

Patient: What are my treatment options?

Doctor: The main treatment is surgery to remove as much of the tumor as safely possible. Surgery helps relieve symptoms and provides tissue for diagnosis. After surgery, depending on the tumor grade and how much we could remove, we may recommend radiation therapy to target any remaining tumor cells. Chemotherapy is less commonly used but may be considered in some cases.

Patient: What are the risks or side effects of surgery and radiation?

Doctor: Surgery carries risks such as bleeding, infection, and possible neurological changes depending on the tumor location. Our surgical team will take every precaution to minimize these. Radiation can cause fatigue, skin irritation, and sometimes cognitive effects, but we use advanced techniques to reduce side effects.

Patient: How will this affect my daily life?

Doctor: Many patients return to their normal activities after treatment, though some may need rehabilitation or support depending on symptoms. We’ll work with a multidisciplinary team including physical therapists and counselors to support you.

Patient: Will I need follow-up care?

Doctor: Yes, regular follow-up with MRI scans is important to monitor for any recurrence. We’ll schedule these visits and coordinate your care with specialists experienced in ependymoma.

Patient: Are there clinical trials or new treatments?

Doctor: There are ongoing clinical trials exploring targeted therapies and improved radiation techniques. We can discuss whether any are suitable for you.

Patient: Thank you, doctor. This helps me understand what to expect.

Doctor: You’re welcome. Please feel free to ask any questions at any time. We’re here to support you throughout your treatment journey.

**Which questions should I ask my doctor?**

You may want to ask your healthcare provider:

## **What grade is the ependymoma?**

* Ependymomas are classified into three WHO CNS grades based on histological and molecular features:
  + Grade 1: Subependymoma (slow-growing, benign)
  + Grade 2: Conventional (classic) ependymoma and myxopapillary ependymoma (now upgraded from grade 1 to grade 2 due to clinical behavior)
  + Grade 3: Anaplastic ependymoma (more aggressive, malignant)
* Molecular subtypes (e.g., ZFTA fusion-positive, YAP1 fusion-positive, posterior fossa group A/B, MYCN-amplified spinal ependymoma) are increasingly important for prognosis but currently are not assigned formal grades in WHO CNS .

## **2. Which type of tumor is it?**

* Ependymoma is a tumor arising from ependymal cells lining the ventricles of the brain or the central canal of the spinal cord.
* Subtypes include:
  + Supratentorial ependymomas (e.g., ZFTA fusion-positive, YAP1 fusion-positive)
  + Posterior fossa ependymomas (Group A and B)
  + Spinal ependymomas (classic and MYCN-amplified)
  + Myxopapillary ependymoma (spinal, grade 2)
  + Subependymoma (grade 1, benign)
* The tumor type is defined by anatomical location and molecular profile, which influence behavior and treatment .

## 3**. Which treatments will I need?**

* Surgery is the primary treatment to remove as much tumor as safely possible.
* Depending on the grade and extent of resection, radiation therapy is often recommended postoperatively, especially for grade 2 and 3 tumors or if complete removal is not possible.
* Chemotherapy is less commonly used but may be considered in certain cases, especially for recurrent or high-grade tumors.
* Treatment plans are tailored based on tumor location, grade, molecular subtype, and patient factors .

## 4. **What are the chances the ependymoma comes back after it’s removed?**

* Recurrence risk depends on tumor grade, extent of surgical removal, and molecular subtype:
  + Grade 1 (subependymoma): Low recurrence risk, often cured by surgery alone.
  + Grade 2 (conventional and myxopapillary): Moderate risk of recurrence, especially if resection is incomplete. Myxopapillary ependymomas have a tendency to disseminate and recur.
  + Grade 3 (anaplastic): Higher risk of recurrence and more aggressive behavior.
* Molecular subtypes such as posterior fossa group A and MYCN-amplified spinal ependymomas are associated with worse prognosis and higher recurrence rates.

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**CRANIOPHARYNGIOMA**

**DEFINITION AND DESCRIPTION**

Craniopharyngioma is a rare type of noncancerous brain tumor.

Craniopharyngioma begins as a growth of cells near the brain's pituitary gland. The pituitary gland makes hormones that control many body functions. As a craniopharyngioma slowly grows, it can affect the pituitary gland and other nearby structures in the brain.

Craniopharyngioma can happen at any age, but it occurs most often in children and older adults. Symptoms include changes in vision over time, fatigue, headaches and urinating more often. Children with craniopharyngioma may grow slowly and may be smaller than expected.

Each year, approximately 2 people per 1 million are diagnosed with one of two types of craniopharyngiomas: adamantinomatous and papillary. They typically present in two age groups: in children aged 5 to 14 and in adults aged 50 to 74. Adamantinomatous types can be found in all age groups, whereas papillary subtypes are almost always found in adults.

**How serious is a craniopharyngioma?**

A craniopharyngioma is a serious medical condition that may require life-long medical treatment. About half of all surgically removed tumors come back over time. Craniopharyngiomas cause several medical conditions that remain even after the tumor has been removed.

**Craniopharyngioma and a pituitary adenoma**

Craniopharyngiomas and pituitary adenomas can both affect hormone function. Pituitary adenomas are tumors that come from your pituitary gland, and craniopharyngiomas are located near that gland. Although both tumors are considered benign, craniopharyngiomas generally have a more aggressive nature than pituitary adenomas.

**Symptoms**

Signs and symptoms of craniopharyngioma may include:

* Headaches.
* Vision changes.
* Nausea and vomiting.
* Increased urination.
* Sleepiness.
* Memory troubles.
* Loss of balance.
* Trouble walking.
* Changes in personality or behavior.
* Weight gain and slowed growth in children.

**Causes**

It's not clear what causes craniopharyngioma. Craniopharyngioma begins as a growth of cells near the brain's pituitary gland. The pituitary gland makes hormones that control many body functions.

Craniopharyngioma happens when cells 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 tumor cells, the DNA changes give different instructions. The changes tell the tumor cells to grow and multiply quickly. Tumor cells can keep living when healthy cells die. This causes too many cells.

**Risk factors**

Healthcare professionals haven't found many risk factors for craniopharyngioma. This tumor can happen at any age. But it's more common in children and older adults.

**Diagnosis**

Diagnosing a craniopharyngioma usually starts with a medical history review and a discussion of symptoms. Tests used to diagnose a craniopharyngioma include:

* **Neurological exam.** During this exam, a healthcare professional tests vision, hearing, balance, coordination, reflexes, and growth and development. This can help show which part of the brain might be affected by the tumor.
* **Blood tests.** Blood tests may reveal changes in hormone levels that show a tumor is affecting the pituitary gland.
* **Imaging tests.** Imaging tests capture pictures of the brain. The pictures can show the size and location of the tumor. Imaging tests include X-rays, CTs and MRIs. In certain situations, other tests might be needed.

**Treatment**

Craniopharyngioma treatment often starts with surgery. When possible, surgeons remove all of the tumor. Sometimes the craniopharyngioma can't be removed completely. Surgeons may remove as much of the craniopharyngioma as is safe.

Radiation therapy may be used after surgery to treat any tumor cells that remain. Using surgery and radiation together often provides good tumor control. This approach also helps lower the risk of complications after surgery.

Other treatments, such as chemotherapy and targeted therapy, might be options in certain situations.

**Surgery**

Most people with craniopharyngioma have surgery to remove all or most of the tumor. What type of surgery you have depends on the location and size of the tumor.

* **Open craniopharyngioma surgery.** Also called a craniotomy, this operation involves opening the skull to access the tumor.
* **Minimally invasive craniopharyngioma surgery.** Also called a transsphenoidal procedure, this operation uses special surgical tools inserted through the nose. The tools go through a natural passage to get to the tumor. This approach minimizes the effect on the brain.

When possible, surgeons remove the entire tumor. However, there are often many delicate and important structures nearby. This means that surgeons sometimes can't remove the entire tumor. To ensure a good quality of life after the operation, surgeons remove as much of the tumor as possible. Other treatments may be used after surgery.

Surgeons do the operation in a way that avoids hurting nearby structures during the operation. Surgeons take care to reduce the risk of vision problems. They work to minimize damage to the hypothalamus. The hypothalamus helps with many functions, including controlling appetite and alertness.

Surgery is sometimes used to relieve a fluid backup on the brain, called hydrocephalus. A tube can be placed to drain the fluid. Often the tube is temporary. Sometimes a permanent tube is needed. A permanent tube, called a shunt, can drain the brain fluid to the abdomen.

**Radiation therapy**

Radiation therapy uses powerful energy beams to control tumor cells. The energy can come from X-rays, protons or other sources.

Radiation therapy is often used after surgery to treat any tumor cells that are left.

Types of radiation therapy for craniopharyngioma include:

* **External beam radiation therapy.** During external beam radiation therapy, you lie on a table while a machine moves around you. The machine directs radiation to precise points on your body.

Specialized external beam radiation technology allows your healthcare team to carefully shape and aim the radiation beam. This helps to deliver treatment to the tumor cells and reduces the chances of hurting healthy tissue. These technologies include proton beam therapy and intensity-modulated radiation therapy, also called IMRT.

* **Stereotactic radiosurgery.** Stereotactic radiosurgery is an intense form of radiation treatment. It aims many beams of radiation from many angles at the tumor. Stereotactic radiosurgery treatment is typically completed in one or a few treatments.
* **Brachytherapy.** Brachytherapy involves placing radioactive material directly into the tumor where it can radiate the tumor from the inside.

**Chemotherapy**

Chemotherapy uses medicines to kill tumor cells. Chemotherapy can be injected directly into the tumor so that the treatment reaches the target cells. This makes it less likely to damage nearby healthy tissue.

**Treatment for papillary craniopharyngioma**

Targeted therapy medicines might be a treatment option for one type of craniopharyngioma called papillary craniopharyngioma. This type isn't common. In adults, about one out of every three craniopharyngiomas is the papillary type.

Targeted therapy uses medicines that attack specific chemicals in the tumor cells. By blocking these chemicals, targeted treatments can cause tumor cells to die.

Nearly all papillary craniopharyngioma cells contain a change in their DNA called the BRAF gene. Targeted therapy aimed at this change may be a treatment option. Lab testing can show whether your craniopharyngioma contains papillary cells. Tests also can tell whether those cells have the BRAF gene change.

**What are common surgery side effects?**

Surgery to remove craniopharyngiomas can be very challenging. First, these tumors develop near delicate nerves and your pituitary gland, which are at risk for damage. Second, removing a craniopharyngioma is like pulling a sticky label off an envelope without tearing the envelope. That’s because these tumors tend to cling to your pituitary gland and the nerves that control vision. Some healthcare providers believe surgery to remove these tumors may cause as much damage as the tumors. So, it’s important to understand what the goal of surgery will be ahead of time and what side effects may be expected.

**Outlook / Prognosis**

Many people live for years after treatment. But these tumors often come back (recur). Overall, as many as 17% of tumors that are completely removed during surgery come back. That number increases to 25% to 63% for partially removed tumors. Most craniopharyngiomas that return will do so within three years after surgery.

**Prevention**

These tumors can’t be prevented. These tumors develop due to changes in your or your child’s cells that happened while your or your child’s body was being formed.

**Living With**

**Some healthcare providers consider a craniopharyngioma a chronic condition that needs long-term care and monitoring; here’s why:**

* You or your child may need additional surgery to remove a recurring tumor.
* If the tumor or surgery caused problems with your or your child’s pituitary or hypothalamus, you or your child may need hormone replacement therapy.
* Many children who have tumor-related obesity, called hypothalamic obesity, have an increased risk for other health problems. If your child has hypothalamic obesity, you may need support and guidance so you can help your child make good food choices and get regular exercise.

**When should I/my child see a healthcare provider?**

Chances are you or your child will be coping with craniopharyngioma for years to come. These tumors tend to come back, and many times, treatment can’t make all symptoms go away. Here are some things to consider as you plan for your/your child’s care:

* You or your child will need to see healthcare providers annually so they can monitor your or your child’s overall health.
* You or your child’s healthcare providers likely will order annual scans, typically MRIs, to check for recurring tumors.
* You or your child probably will need help managing conditions like hormone deficiencies and vision problems that surgery didn’t cure.

## 

## **Diagnostic Considerations**

Different considerations need to be kept in mind when assessing a sellar/suprasellar lesion. Clinical manifestations can be broad, including brain stem syndromes (from mass effect or vascular etiology), endocrine disturbances, visual changes, seizures, etc. Different etiologies mandate different preoperative evaluation (ie, MRI, vascular imaging, endocrine profile, visual fields evaluation, etc.).

Tumors to consider in the differential diagnosis include the following:

* Brainstem glioma
* Epidermoid and dermoid tumor
* Germ cell tumor (mainly in children and young adults)
* Hypothalamic-optic pathway glioma
* Low-grade astrocytoma
* Medulloblastoma
* Meningioma
* Metastasis (mainly in the adult population)
* Hypothalamic hamartoma
* Pituitary tumor
* Primitive neuroectodermal tumors of the central nervous system(CNS)

The following infectious or inflammatory processes can be considered in the differential diagnosis:

* Histiocytosis X
* Infundibulitis
* Lymphocytic hypophysitis
* Sarcoidosis
* Syphilis
* Tuberculosis

Vascular malformations to consider in the differential diagnosis include the following:

* Carotid-cavernous fistula
* Cavernous sinus hemangioma
* Giant suprasellar carotid aneurysm

Other congenital defects to consider in the differential diagnosis include the following:

* Arachnoid cyst
* Rathke cleft cyst

## 

## **Differential Diagnoses**

* Cavernous Sinus Syndromes
* Leptomeningeal Carcinomatosis (Metastasis) Imaging
* Lyme Disease
* Migraine Headache
* Migraine Variants
* Multiple Sclerosis
* Primary CNS Lymphoma
* Pseudotumor Cerebri
* Tolosa-Hunt Syndrome
* Tuberculous Meningitis
* Vascular Surgery for Arteriovenous Malformations

## **Epidemiology**

### Occurrence

Data from the Central Brain Tumor Registry of the United States (CBTRUS), collected between 2016 and 2020 (corresponding to the 2023 report),found the following results:

* Overall incidence was 0.19 per 100,000 person years
* Incidence rates of craniopharyngioma for African Americans exceed those observed for Caucasian, AIAN, and API
* Distribution by age is bimodal with one peak incidence in childhood (0–19 years) and another in adulthood between the ages of 45 and 84 years with a higher peak for ages 65–74 years

Overall, craniopharyngiomas account for 0.5% of intracranial tumors and 13% of suprasellar tumors. In the United States, the estimated incidence rate per 100,000 per year for the pediatric population (0–14 years) is 0.2, while it is 0.13 for ages 15–39 years. Incidence reaches up to 0.22 for patients older than 40 years.

### Race-, sex-, and age-related demographics

There is an increased incidence in Black patients versus White patients (0.26 vs 0.17 cases per 100,000 people). No differences are seen between Hispanic and non-Hispanic people. A higher five-year total incidence was observed in males compared to females (1102 cases vs 987 cases).

Craniopharyngiomas have a bimodal age distribution pattern, with a peak between ages 5 and 14 years and in adults older than 65 years, although there are reports involving all age groups.

**Craniopharyngioma Procedures and Treatment Timeline**

## 1. Initial Evaluation and Diagnosis

* Neurological exam to assess vision, coordination, reflexes, and hormone function.
* Imaging studies: MRI (with and without contrast) and CT scan (to detect calcifications).
* Endocrine evaluation to assess pituitary/hypothalamic function.

Timeline: Usually completed within days to a couple of weeks after symptom onset.

## 2. Surgical Treatment

* Goal: Maximal safe resection of the tumor while preserving critical structures (optic nerves, hypothalamus, pituitary).
* Approaches:
  + Open craniotomy: Traditional skull opening for large or complex tumors.
  + Transsphenoidal (minimally invasive): Through the nose for smaller, midline tumors.
* Complete removal is ideal but often limited by tumor location and adherence to vital structures.
* Surgery may last 1–3 hours depending on complexity.

Timeline: Surgery is typically scheduled soon after diagnosis, often within 1–4 weeks.

## 3. Postoperative Care and Imaging

* Early postoperative MRI (within 48–72 hours) to assess extent of resection and residual tumor.
* Monitor neurological status and manage complications.
* Begin endocrine hormone replacement if needed.

Timeline: Imaging and recovery monitoring occur immediately after surgery.

## 4. Adjuvant Radiation Therapy

* Recommended if subtotal resection or residual tumor remains, or for recurrent disease.
* Types:
  + Fractionated conformal radiotherapy (daily sessions over 5–6 weeks).
  + Proton beam therapy (preferred in children to minimize collateral damage).
  + Radiosurgery (single high-dose treatment) in select cases.
* Radiation helps control tumor growth and delay recurrence.

Timeline: Usually starts 4–6 weeks after surgery to allow healing.

## 5. Medical and Supportive Therapies

* Lifelong hormone replacement therapy due to pituitary/hypothalamic damage (adrenal, thyroid, gonadal, growth hormones).
* Cyst-directed therapies (e.g., intracystic interferon-α or bleomycin) for recurrent cystic tumors.
* Targeted therapy: For papillary craniopharyngioma with BRAF V600E mutation, BRAF/MEK inhibitors (vemurafenib, dabrafenib + trametinib) can shrink tumors, especially if unresectable or recurrent.

## 6. Follow-Up and Long-Term Management

* Regular MRI scans every 3–6 months initially, then annually if stable.
* Ongoing endocrine evaluation and management.
* Neurocognitive and psychosocial support as needed.

## **Doctor-Patient Conversation: Craniopharyngioma**

Doctor: Hello, I want to discuss the results of your child’s scans and what we know about the tumor. How are you feeling today?

Patient (Parent): I’m very worried. What did the tests show?

Doctor: Your child has a tumor called a craniopharyngioma. This is a slow-growing tumor that arises near the pituitary gland, close to important structures like the optic nerves and hypothalamus. It can cause symptoms like headaches, vision problems, and hormonal imbalances.

Patient: Is it cancer? How serious is it?

Doctor: Craniopharyngiomas are benign, meaning they are not cancerous, but they can cause serious problems because of their location. They can press on nearby brain structures and affect hormone production, so we treat them carefully to control growth and preserve function.

Patient: What are the treatment options?

Doctor: The main treatment is surgery to remove as much of the tumor as safely possible. Complete removal is ideal but can be challenging because the tumor often sticks to vital brain areas. Sometimes we remove part of the tumor and then use radiation therapy to control any remaining tumor cells.

For cystic parts of the tumor, we might also consider intracystic treatments, like injecting medications or radioisotopes directly into the cyst to reduce its size.

Patient: What are the risks or side effects?

Doctor: Surgery can have risks like damage to the optic nerves or hypothalamus, which can affect vision or hormone balance. Radiation can cause fatigue and sometimes affect hormone function or cognition, but we use precise techniques to minimize side effects.

Because the tumor and treatment can affect hormone production, your child will likely need lifelong hormone replacement therapy and regular follow-up with endocrinology.

Patient: How long does treatment take? What happens after?

Doctor: Surgery is usually the first step, followed by recovery and then radiation therapy if needed, which lasts about 5–6 weeks. After treatment, we monitor your child regularly with MRI scans and hormone tests to watch for any recurrence or late effects.

Patient: Are there any new treatments or clinical trials?

Doctor: For certain tumor types, especially papillary craniopharyngiomas with specific mutations, targeted therapies like BRAF inhibitors may be options, especially if surgery or radiation can’t fully control the tumor.

Patient: What should I watch for during and after treatment?

Doctor: Watch for new headaches, vision changes, excessive thirst or urination, or changes in behavior or growth. If any of these occur, please contact us immediately.

Patient: Thank you, Doctor. This helps me understand what to expect.

Doctor: You’re welcome. We have a multidisciplinary team including neurosurgeons, endocrinologists, radiation oncologists, and support staff to guide you through every step. Please don’t hesitate to ask any questions at any time.

**Genomic Data of Craniopharyngiomas**

## 1. Adamantinomatous Craniopharyngioma (ACP)

* Key Mutation:
  + Frequent mutations in the CTNNB1 gene, which encodes β-catenin, particularly in exon 3.
  + These mutations lead to abnormal activation of the WNT/β-catenin signaling pathway, causing nuclear and cytoplasmic accumulation of β-catenin in tumor cells.
* Prevalence:
  + About 60–76% of ACP cases harbor CTNNB1 mutations.
* Genomic Features:
  + Generally stable genomes with occasional focal chromosomal gains or losses (e.g., loss in Xq28).
  + No other recurrent mutations detected in large sequencing panels.
* Clinical Implication:
  + WNT pathway activation is the crucial driver event in ACP pathogenesis.
  + Mutations are clonal and consistent between primary tumors and recurrences.

## 2. Papillary Craniopharyngioma (PCP)

* Key Mutation:
  + Almost all PCPs (~90–95%) harbor the BRAF V600E mutation, a driver mutation activating the RAS/RAF/MEK/ERK signaling pathway.
* Genomic Features:
  + PCPs typically have stable genomes with fewer chromosomal aberrations.
  + BRAF V600E mutation is mutually exclusive with CTNNB1 mutations seen in ACP.
* Clinical Implication:
  + This mutation provides a target for BRAF and MEK inhibitor therapies, which have shown promise in shrinking tumors and reducing treatment side effects.

**What questions should I ask my/my child’s healthcare provider?**

Craniopharyngiomas are rare benign tumors that can cause several challenging medical conditions that may require long-term care. If you or your child have this type of tumor, you may worry about managing this life-long condition. Some questions that may help you as you talk to your or your child’s healthcare provider include:

## **What is a craniopharyngioma?**

A craniopharyngioma is a rare, benign (noncancerous) brain tumor that develops near the pituitary gland at the base of the brain. It arises from embryonic cells near the sellar region, where the pituitary gland sits. The tumor can be solid or cystic (fluid-filled) and grows slowly.

## 2. **Can this tumor cause serious medical problems?**

Yes. Although benign, craniopharyngiomas can cause serious problems because of their location near important brain structures:

* Pituitary gland: Tumor pressure can disrupt hormone production, leading to hormonal imbalances affecting growth, metabolism, puberty, and other body functions.
* Optic nerves and chiasm: Compression can cause vision problems, including loss of peripheral vision or blurry vision.
* Hypothalamus: Damage can cause issues with appetite, weight regulation (hypothalamic obesity), sleep, mood, and body temperature control.
* Cerebrospinal fluid pathways: Blockage can cause hydrocephalus (fluid buildup in the brain), leading to headaches, nausea, vomiting, and in infants, an enlarged head.

## 3. **Why do I or my child have this tumor?**

The exact cause is unknown. Craniopharyngiomas develop from leftover embryonic cells near the pituitary gland that abnormally grow into a tumor. There are no known inherited or environmental causes identified.

## 4**. What are the treatment options?**

* Surgery: The main treatment is to remove as much of the tumor as safely possible, either through the nose (minimally invasive) or an opening in the skull.
* Radiation therapy: Often recommended after surgery if the tumor cannot be completely removed to control growth.
* Hormone replacement: Because the tumor or treatment can affect hormone production, lifelong hormone therapy may be needed.
* Cyst treatments: For cystic tumors, sometimes medications are injected directly into the cyst to reduce its size.
* Targeted therapy: For certain tumor types with specific mutations, targeted drugs may be an option.

## 5. **What are the chances treatment will be successful?**

* Craniopharyngiomas are benign and slow-growing, so treatment can control or remove the tumor.
* However, these tumors often recur even after complete removal, so long-term monitoring is necessary.
* Success depends on tumor size, location, and how much can be safely removed.

## 6. **Will treatment make symptoms go away?**

* Surgery and radiation often improve symptoms caused by tumor pressure, such as headaches and vision problems.
* Hormonal symptoms may improve but often require ongoing hormone replacement.
* Some neurological or hypothalamic symptoms may persist or develop after treatment.

## 7. **What are possible short-term and long-term side effects of treatment?**

* Short-term: Fatigue, headaches, nausea, swelling, infection risk after surgery; skin irritation and fatigue from radiation.
* Long-term: Hormonal deficiencies requiring lifelong replacement, vision changes, cognitive or memory difficulties, hypothalamic obesity, and risk of tumor recurrence.
* Radiation may cause delayed effects on brain function or hormone production.

## 8. **What happens if the tumor comes back?**

* Recurrence is common and may require further surgery, radiation, or other treatments.
* Ongoing monitoring with regular MRI scans is essential to detect recurrence early.
* New or worsening symptoms should prompt immediate medical evaluation

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**Atypical teratoid/rhabdoid tumor (AT/RT)**

An atypical teratoid/rhabdoid tumor (AT/RT) is a fast-growing central nervous system cancer. Cancer cells begin growing in your brain or spinal cord. Around half of all AT/RT cases start in your cerebellum or brainstem. It most often affects children.

Symptoms of AT/RT can come on suddenly. It may seem like your child has a common illness at first, but their symptoms don’t get better with time or traditional therapies. A healthcare provider will recommend testing to understand why your child isn’t feeling well. After diagnosing AT/RT, they’ll offer treatment options specific to your child’s situation.

This type of tumor has a generally poor outcome. It spreads quickly and can be hard to remove. As a result, it may shorten your child’s life expectancy. However, not all cases have a poor outcome. Researchers are studying new treatment options every day to help improve your child’s chance of survival.

There are a lot of uncertainties when you learn about a cancer diagnosis, especially a rare cancer like AT/RT. Remember that your child’s care team will be with you throughout their journey. Support is available for families and caregivers as well.

AT/RT is a rare type of brain cancer that affects your central nervous system (CNS). Your CNS includes your brain and spinal cord.

In the United States, one study estimated that 470 people are living with AT/RT. This equals about 73 people who receive this diagnosis each year. Only 4 people out of 73 are adults.

**Symptoms and Causes**

The signs and symptoms of AT/RT vary based on your age and where the tumor is in your body. The following symptoms may happen suddenly and get worse quickly:

* Headaches (usually in the morning, which go away after vomiting).
* Nausea and vomiting.
* Fatigue.
* Activity level changes (low energy).
* Difficulty with balance, coordination and walking.

Parents or caregivers may notice that infants have a larger head size because of this tumor, but it may not be as noticeable in older children.

**What causes AT/RT?**

A genetic change (mutation) to either the *SMARCB1* or *SMARCA4* gene causes AT/RT. These are tumor suppressor genes. They make a protein that regulates when and how often cells grow. A change to one of these genes can cause cells to grow uncontrollably, which leads to tumors.

**Is AT/RT genetic?**

Yes, some cases of AT/RT are genetic. You can inherit the gene change (germline mutation) that causes the tumor from your biological parents. But most cases aren’t inherited. Instead, the gene change happens randomly (sporadically) without a history in your biological family.

**Risk factors for AT/RT?**

Most AT/RTs affect children younger than 3 years old. But it can happen to both children and adults at any age.

**Diagnosis and Tests**

A healthcare provider will diagnose AT/RT after a physical exam, a neurological exam and testing. During the exams, your child’s provider will learn more about their symptoms, medical history and family medical history.

Testing may include:

* MRI.
* Lumbar puncture.
* Genetic testing.
* Biopsy.

**Management and Treatment**

Your child’s healthcare provider may recommend the following to treat AT/RT:

* **Removal surgery**: A neurosurgeon will surgically remove as much of the tumor as possible. Your child may need chemotherapy and radiation therapy after surgery to destroy any remaining cancer cells.
* **Chemotherapy**: Chemotherapy is a medication that destroys cancer cells or stops them from dividing (creating more cells). Your child’s provider may treat AT/RT with oral (by mouth) medications or medicine injected into your child’s vein or muscle (systemic chemotherapy). Or your child’s provider will inject chemotherapy medication into the fluid surrounding your child’s spinal cord (intrathecal chemotherapy).
* **Radiation therapy**: Radiation therapy uses high-powered X-rays to destroy cancer cells or prevent them from growing. A machine will direct beams of radiation toward the tumor in your child’s body. Children younger than 3 years old may need a low dose of radiation, as it can affect their growth and development.
* **Stem cell transplantation**: After high-dose chemotherapy, your child may undergo stem cell transplantation to replace cells they lost. Before chemotherapy, your child’s provider will remove and store some of your child’s stem cells. They’ll intravenously (through a needle into a vein) put these cells back into your child’s body after chemotherapy.
* **Targeted therapy**: This is a newer type of treatment currently in clinical trials for AT/RT. Certain medications prevent components of a cell from doing their job in your child’s body, which can stop cancer cells from growing and multiplying.
* **Immunotherapy**: Immunotherapy is in clinical trials for AT/RT. It helps your child’s immune system fight cancer.
* **Palliative care**: Palliative care provides symptom relief, comfort and support to your child to help improve their quality of life.

A healthcare provider will determine what type of treatment they recommend after reviewing diagnostic and imaging tests. Your child may need more than one type of treatment. Follow-up care will be important throughout your child’s life. After treatment, they’ll likely need additional testing to ensure the treatment worked and that cancer hasn’t returned.

**Who is on my child’s care team?**

You’ll likely see a lot of different healthcare providers during treatment for AT/RT. Your child’s care team may include:

* Pediatricians or primary care physicians.
* Neurosurgeons.
* Radiation oncologists.
* Neurologists.
* Genetic counselors.

**Are there side effects of the treatment?**

Side effects are possible with all types of AT/RT treatment. Your child’s provider will explain what the potential side effects are and what to look out for during treatment. Some side effects may happen during treatment, while others may not appear until months after. If you have any questions, let your child’s provider know.

**Treatment Drugs for Atypical Teratoid/Rhabdoid Tumor (AT/RT) and Their Side Effects**

## Common Chemotherapy Drugs Used in AT/RT Treatment

| **Drug** | **Role in AT/RT Treatment** | **Common Side Effects** |
| --- | --- | --- |
| Vincristine | Microtubule inhibitor, often part of multi-agent regimens | Peripheral neuropathy (numbness, tingling), constipation, hair loss |
| Cisplatin | Platinum-based agent, used for tumor cell killing | Kidney toxicity, hearing loss, nausea, vomiting, neuropathy |
| Cyclophosphamide | Alkylating agent, used in combination regimens | Bone marrow suppression, nausea, hemorrhagic cystitis, fatigue |
| Etoposide | Topoisomerase inhibitor, part of intensive protocols | Bone marrow suppression, nausea, hair loss, risk of secondary leukemia |
| Methotrexate | Antimetabolite, sometimes used in high doses | Mouth sores, liver toxicity, bone marrow suppression, kidney toxicity |
| Ifosfamide | Alkylating agent, used in some regimens | Bone marrow suppression, kidney toxicity, neurotoxicity, nausea |
| Temozolomide | Oral alkylating agent, sometimes used | Fatigue, nausea, low blood counts |

## Radiation Therapy

* Often combined with chemotherapy after surgery in children over 3 years old.
* Side effects include fatigue, skin irritation, hair loss, cognitive changes, and possible long-term neurological effects.

## General Side Effects of Chemotherapy and Radiation in AT/RT

* Bone marrow suppression: Low blood counts leading to anemia (fatigue), neutropenia (infection risk), and thrombocytopenia (bleeding risk).
* Nausea and vomiting: Common with many chemo drugs; managed with antiemetics.
* Neuropathy: Especially with vincristine and cisplatin, causing numbness or tingling in hands and feet.
* Hair loss: Temporary but common.
* Kidney and hearing damage: Especially with cisplatin and ifosfamide; requires monitoring.
* Fatigue: Common during and after treatment.
* Mouth sores and gastrointestinal symptoms: From drugs like methotrexate.
* Risk of infections: Due to immune suppression; requires close monitoring.

## Management and Monitoring

* Side effects are managed with supportive care, including medications for nausea, growth factors for blood counts, hydration for kidney protection, and physical therapy for neuropathy.
* Regular blood tests and hearing tests are essential during treatment.
* Dose adjustments may be necessary based on tolerance.

**Outlook / Prognosis**

As AT/RT is an aggressive type of cancer, it may lead to early death if treatment doesn’t remove it from your child’s body. This varies significantly from person to person. For example, a cure is possible if surgeons can completely remove the tumor during a procedure.

The outlook varies based on several factors, including:

* Your child’s age.
* Their genetic inheritance.
* How much of the tumor can safely be removed during surgery.
* If the cancer spread to other parts of your child’s body.

Your healthcare provider will give you the most accurate information about your child’s outlook (prognosis). If you have any questions about what to expect, talk to your child’s care team.

**What is the survival rate and cure rate for AT/RT?**

Because AT/RT is a rare type of cancer, there isn’t enough data available to determine the survival rate and cure rate for this condition. Your child’s provider will have the most up-to-date information for your child’s situation.

**Prevention**

There isn’t a way to prevent AT/RT. If you plan on expanding your family, you may choose to speak with a counselor about genetic testing to learn more about your risk of having a child with a gene change that could cause AT/RT.

**DIFFERENTIAL DIAGNOSIS**

* Medulloblastoma (most common main differential, especially in young children)
* Supratentorial Primitive Neuroectodermal Tumor (SPNET)
* Ependymoma
* Teratoma
* Choroid Plexus Tumors (papilloma or carcinoma)
* Pilocytic Astrocytoma
* Desmoplastic Infantile Ganglioglioma
* Schwannoma (especially in cerebellopontine angle region)
* Rhabdoid Meningioma
* Malignant Glioma
* Germinoma and other Germ Cell Tumors
* Anaplastic Meningioma
* Other CNS Embryonal Tumors
* Pituitary Adenoma (in sellar region adult cases)
* Lymphoma (CNS lymphoma)

**Epidemiology of Atypical Teratoid/Rhabdoid Tumors (AT/RT)**:

* Incidence and Age:
  + AT/RTs are rare but highly aggressive embryonal tumors of the central nervous system (CNS).
  + They account for about 20% of CNS tumors in children under 3 years old.
  + The median age at diagnosis is around 1 to 1.5 years (12–16 months), with the highest incidence in children younger than 3 years, especially under 1 year of age.
  + The overall age-adjusted incidence rate is approximately 0.07 per 100,000 children, with the highest rates in infants under 1 year (0.54 per 100,000) and 1-year-olds (0.41 per 100,000).
  + AT/RT is the most common malignant CNS tumor in children less than one year old.
* Gender and Race:
  + Slightly more common in males (about 56%) than females.
  + More frequently diagnosed in Caucasians (around 59%).
  + No significant difference by race or Hispanic ethnicity in some studies, but some demographic variations exist.
* Tumor Location:
  + Most common primary sites include the cerebellum (17.8%), ventricles (16.1%), and frontal lobe (12.6%).
  + Can occur throughout the CNS, including supratentorial and infratentorial regions.
* Survival and Mortality:
  + Mean overall survival is approximately 3.2 years, with high mortality rates (cancer-specific mortality around 56%).
  + Adult cases are very rare (only a few percent of total cases).
* Risk Factors:
  + Some studies suggest associations with low birth weight and preterm birth.
  + No clear environmental or hereditary causes identified.
* Prevalence:
  + Approximately 470 people living with AT/RT in the United States, with about 50 adults affected.

**Genomic Data of Atypical Teratoid/Rhabdoid Tumors (AT/RT):**

* Key Genetic Drivers:
  + The vast majority (~95%) of AT/RTs are caused by bi-allelic inactivating mutations or deletions in the SMARCB1 gene (also known as INI1), a tumor suppressor gene located on chromosome 22q11.2.
  + A smaller subset (~5%) harbor mutations in SMARCA4, another tumor suppressor gene encoding the BRG1 protein, part of the SWI/SNF chromatin remodeling complex.
* Molecular Subgroups (SMARCB1-mutated AT/RT):  
  Based on DNA methylation and transcriptomic profiling, SMARCB1-mutated AT/RTs are classified into three distinct molecular subgroups with differing clinical and biological features:
  + ATRT-TYR: Typically infratentorial (posterior fossa), occurs in younger children (<1 year), characterized by overexpression of melanosomal markers (e.g., TYR, DCT).
  + ATRT-SHH: Enriched for Sonic Hedgehog pathway activation, intermediate age group, distinct gene expression profile.
  + ATRT-MYC: Often supratentorial, older children and adults, characterized by MYC oncogene activation and poorer prognosis.
* SMARCA4-mutated AT/RT:
  + These tumors form a distinct molecular subgroup separate from SMARCB1-mutated AT/RTs.
  + They are associated with a higher frequency of germline mutations, younger age at diagnosis, and generally worse prognosis.
  + Their molecular profile differs significantly from SMARCB1-mutated AT/RTs and other SMARCA4-deficient tumors.
* Germline Mutations and Predisposition:
  + Approximately one-third of AT/RT patients have germline mutations in SMARCB1 or SMARCA4, causing Rhabdoid Tumor Predisposition Syndrome (RTPS).
  + These germline mutations predispose to early-onset rhabdoid tumors in the CNS, kidney, and soft tissues.
* Genomic Landscape:
  + AT/RTs generally have a low tumor mutational burden aside from SMARCB1/SMARCA4 alterations.
  + Common cytogenetic changes include monosomy or deletion of chromosome 22.
  + DNA methylation profiles and gene expression signatures are stable and subgroup-specific, aiding diagnosis and prognosis.
* Functional Impact:
  + Loss of SMARCB1 or SMARCA4 disrupts the SWI/SNF chromatin remodeling complex, leading to altered gene expression and uncontrolled tumor growth.

## **Doctor-Patient Conversation: Atypical Teratoid/Rhabdoid Tumor (AT/RT)**

Doctor: Hello, I want to talk with you about the diagnosis we have from your child’s tests. How are you feeling today?

Parent: I’m very worried, doctor. What did the tests show?

Doctor: Your child has a tumor called an Atypical Teratoid/Rhabdoid Tumor, or AT/RT. It’s a rare and aggressive brain tumor that mostly affects very young children. It grows quickly, but we have treatment options that can help.

Parent: What causes this tumor? Is it cancer?

Doctor: AT/RT is a malignant tumor, meaning it is cancerous. It arises because of changes in certain genes—most commonly a gene called SMARCB1—which normally help control cell growth. When this gene doesn’t work properly, cells grow uncontrollably and form a tumor.

Parent: What are the treatment options?

Doctor: Treatment usually involves a combination of surgery to remove as much of the tumor as possible, followed by radiation therapy and chemotherapy. The exact plan depends on your child’s age, the tumor’s size and location, and whether it has spread. For very young children, we try to balance effective treatment with minimizing side effects.

Parent: What are the chances of success?

Doctor: AT/RT is challenging to treat, but advances in therapy have improved outcomes. Survival depends on several factors, including how much of the tumor we can remove and how well your child responds to chemotherapy and radiation. Some children do very well, especially with aggressive, multimodal treatment.

Parent: Will the treatment make my child’s symptoms go away?

Doctor: Treatment often helps reduce symptoms caused by the tumor, like headaches or neurological problems. However, some symptoms related to brain function or hormone balance may persist or require ongoing management.

Parent: What are the possible side effects of treatment?

Doctor: Chemotherapy and radiation can cause side effects like fatigue, nausea, hair loss, and low blood counts, which increase infection risk. Radiation can also affect brain development, so we use careful planning to minimize this. Surgery carries risks depending on tumor location but is necessary to control the tumor.

Parent: What happens if the tumor comes back?

Doctor: Unfortunately, AT/RT can recur. If that happens, we may consider additional treatments, including more chemotherapy, radiation, or clinical trials of new therapies. Regular follow-up with MRI scans is essential to detect any recurrence early.

Parent: Are there clinical trials or new treatments available?

Doctor: Yes, there are ongoing clinical trials exploring new drugs and treatment combinations. We will discuss if any are suitable for your child.

Parent: Thank you, doctor. This helps me understand what to expect.

Doctor: You’re welcome. We have a multidisciplinary team including surgeons, oncologists, nurses, social workers, and child life specialists to support your family throughout treatment. Please ask any questions at any time.

**What questions should I ask my child’s healthcare provider?**

You probably have a lot of questions after learning about AT/RT. Be sure to ask your child’s provider:

## **Where is the tumor in my child’s body?**

* AT/RT is a fast-growing, malignant tumor of the central nervous system (CNS), meaning it can be located in the brain or spinal cord.
* In children, about half of AT/RTs occur in the cerebellum or brainstem (the posterior fossa region), which controls movement, balance, and vital functions.
* Other tumors may arise in the supratentorial brain regions (cerebral hemispheres, hypothalamus, pineal region) or spinal cord, especially in older children.
* Tumors can sometimes spread through the cerebrospinal fluid to other CNS areas.

## 2. **What type of treatment do you recommend?**

* Treatment usually involves a multimodal approach:
  + Surgery to remove as much of the tumor as safely possible.
  + Chemotherapy, often intensive and multi-agent, to target remaining tumor cells.
  + Radiation therapy, typically given after surgery and chemotherapy, especially in children older than 3 years.
* The exact treatment plan depends on your child’s age, tumor location and size, and overall health.
* Clinical trials or newer targeted therapies may be options depending on the case.

## 3. **Are there side effects of treatment?**

* Yes, treatment side effects can include:
  + Short-term: Fatigue, nausea, vomiting, hair loss, low blood counts leading to infection risk, neuropathy (nerve damage), and skin irritation from radiation.
  + Long-term: Possible effects on brain development, hormone function, cognitive abilities, hearing, and growth.
* Supportive care and monitoring are essential to manage these side effects.

## 4. **How will treatment affect my child’s growth and development?**

* Because AT/RT and its treatment affect the brain and nervous system, there can be impacts on:
  + Physical growth, especially if the pituitary gland or hypothalamus is involved.
  + Cognitive development, including learning and memory.
  + Motor skills and coordination, depending on tumor location and treatment effects.
* Early intervention with rehabilitation, hormone replacement, and educational support can help improve outcomes.

## **5. What’s my child’s prognosis?**

* AT/RT is an aggressive tumor with a median age at diagnosis around 1 to 1.5 years.
* Prognosis depends on factors like tumor location, extent of surgical removal, response to chemotherapy and radiation, and whether the tumor has spread.
* Despite intensive treatment, AT/RT remains challenging to cure, with a 3-year overall survival rate around 25–40% in many studies.
* Advances in treatment and supportive care are improving outcomes over time.

REFERENCES

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[Atypical Teratoid/Rhabdoid Tumor (AT/RT): What It Is](https://my.clevelandclinic.org/health/diseases/atrt-cancer#overview)

**ASTROCYTOMAS**

**DEFINITION AND DESCRIPTION**

Astrocytomas are tumors that develop in your central nervous system (CNS) that grow from star-shaped astrocyte cells. They usually develop in your brain but can develop in your spinal cord as well. Astrocytomas can be benign (noncancerous) or malignant (cancerous).

Astrocytes are glial cells (the type of cells that provide supportive tissue in your brain). Other glial cells include oligodendrocytes and ependymal cells. Astrocytoma is the most common glioma. A glioma is a tumor that forms when glial cells grow out of control.

Healthcare providers use grades to describe different types of astrocytomas. They don’t use a staging system as they do for many other types of cancer.

**Types of astrocytoma**

Astrocytomas may be cancerous or noncancerous. The World Health Organization (WHO) categorizes astrocytomas into four grades. The grades depend on how fast astrocytomas grow and the likelihood that they’ll spread to (infiltrate) nearby brain tissue. Grade 1 astrocytomas are the mildest, while grade 4 astrocytomas are the most aggressive.

**Noncancerous astrocytomas**

Grade 1 astrocytomas, which are noncancerous, include:

* **Pilocytic astrocytoma**: This is a slow-growing tumor that doesn’t tend to spread. It’s the most common grade 1 astrocytoma. It’s benign and doesn’t require chemotherapy or radiation therapy after it’s surgically removed. Pilocytic astrocytomas most often develop in your cerebellum.
* **Pleomorphic xanthoastrocytoma**: This tumor usually grows slowly and most often develops in your temporal lobe. It often causes seizures. Surgery usually cures this type of brain tumor.
* **Subependymal giant cell astrocytoma (SEGA)**: This tumor mainly develops in children who have tuberous sclerosis, a genetic condition. It grows inside ventricles, which are fluid-filled spaces deep in your brain. Surgery usually cures it.

**Cancerous astrocytomas**

Cancerous astrocytomas include:

* **Grade 2 astrocytomas**: These astrocytomas tend to spread to nearby brain tissue. Because of this, surgery alone might not be enough to treat them.
* **Grade 3 astrocytomas**: These astrocytomas are more aggressive than grade 2 astrocytomas and often present as a progression from grade 2 astrocytomas. Surgery alone never cures these tumors. They require radiation and almost always require chemotherapy.
* **Glioblastomas**: These are grade 4 astrocytomas. They’re the most common form of astrocytoma and the most aggressive — they grow and spread rapidly. They can either present as a cancerous progression from a previously existing lower-grade astrocytoma (10% of cases) or begin as a grade 4 tumor (90% of cases).

Astrocytomas can affect anyone, but different grades tend to affect people at different ages:

* Grade 1 astrocytomas most often affect children and teens.
* Astrocytomas, grade 2 most often affect adults between 20 and 60.
* Astrocytomas, grade 3 most often affect adults between 30 and 60.
* Glioblastoma (grade 4 astrocytoma) most often affects adults between 50 and 80.

Grade 3 and 4 astrocytomas are more likely to affect men.

Different grades of astrocytoma are more common than others:

* Grade 1 astrocytomas account for 2% of all brain tumors.
* Grade 2 astrocytomas account for 2% to 5% of all brain tumors.
* Grade 3 astrocytomas account for 4% of all brain tumors.
* Grade 4 astrocytomas (glioblastomas) account for 24% of all brain tumors.

In adults, glioblastoma (grade 4 astrocytoma) is the most common type of brain cancer.

**Symptoms and Causes**

The symptoms of astrocytoma can vary based on its size and location. Common symptoms include:

* Headaches.
* Nausea and vomiting.
* Seizures.
* Altered mental status, such as delirium or dementia.
* Memory loss.
* Other cognitive issues, such as personality changes or mood changes (like depression).
* Fatigue.
* Vision problems.
* Speech problems (aphasia or trouble speaking).
* Motor (movement) issues, such as abnormal reflexes or weakness.

See a healthcare provider as soon as possible if you have these symptoms.

**What causes astrocytoma?**

Researchers don’t know the exact cause of most astrocytomas. The majority of these tumors are sporadic, meaning that they happen randomly. So far, researchers have only identified two known risk factors for astrocytomas: radiation exposure and genetics.

However, recent studies have revealed that a mutation (change) in the *IDH1* gene contributes significantly to the development of low-grade astrocytomas. This gene helps provide energy to your cells. Its mutation results in the production of a chemical called 2-HG, which, over time, builds up inside healthy astrocytes. This buildup causes the cells to become abnormal, causing astrocytomas.

**Radiation exposure and astrocytomas**

Exposure to ionizing radiation, such as from radiation therapy, increases your risk of developing astrocytoma.

For example, children who receive prophylactic (preventive) radiation for acute lymphocytic leukemia (ALL) may be 22 times more likely to develop a central nervous system tumor, such as astrocytoma, within about five to 10 years.

**Genetics and astrocytomas**

The following rare genetic conditions are associated with the development of astrocytomas:

* **Li-Fraumeni syndrome**: This condition happens when something changes in your *TP53* gene. People who have Li-Fraumeni syndrome have a 90% chance of developing one or more types of cancer in their lifetimes, which could include astrocytoma.
* **Neurofibromatosis type 1 (NF1)**: This condition causes abnormal increases in cell growth due to a mutation in a gene that’s supposed to suppress tumor growth. People with NF1 can develop early-onset astrocytomas, peripheral nerve tumors and spots on their skin called café-au-lait spots.
* **Tuberous sclerosis**: This condition causes a variety of medical issues, including epilepsy, developmental delay and tumors throughout your body. Tuberous sclerosis is caused by mutations in two genes: *TSC1* and *TSC2*. Subependymal giant cell astrocytomas (SEGAs) typically only develop in people with tuberous sclerosis.
* **Turcot syndrome**: This condition results when there are mutations in several genes that suppress tumor growth. Turcot syndrome often involves growths (polyps) in your intestinal tract and one or more brain or spinal cord tumors, such as astrocytoma.

**Diagnosis and Tests**

It can be difficult for healthcare providers to detect or suspect astrocytomas, as their symptoms are similar to other neurological conditions.

Regardless, your provider will ask about your symptoms and medical history. They’ll likely perform a neurological exam. This can help determine where in your brain or spinal cord the issue may be.

Your provider may order a brain imaging test. Magnetic resonance imaging (MRI) is the best imaging test for finding and diagnosing astrocytoma. If you’re unable to have an MRI scan due to having a pacemaker or joint implant, a computed tomography (CT scan) is the next best option.

If something abnormal appears on the brain imaging test, your provider will most likely recommend a biopsy or resection (tumor removal) to determine the diagnosis.

**Management and Treatment**

Surgery can cure most grade 1 astrocytomas if your neurosurgeon can safely remove the entire tumor. Very rarely, surgery may also cure some grade 2 astrocytomas.

There’s no cure for grade 3 and grade 4 astrocytomas, as they grow and spread quickly. But radiation therapy and some medications can help slow their growth and help with symptoms.

**How is astrocytoma treated?**

Astrocytoma treatment depends on several factors, including:

* The tumor’s location, size and type.
* Your age.
* Your overall health.

Several specialists will work together to determine the best treatment plan for you. They may include:

* Neurologists.
* Neurosurgeons.
* Radiation oncologists.
* Medical oncologists.

The main forms of treatment for astrocytomas are:

* Surgery.
* Radiation therapy.
* Adjuvant chemotherapy.
* Tumor-treating fields (for glioblastomas).

There may also be clinical trials that you can participate in.

**Surgery for astrocytomas**

Surgery is the first step in the treatment of astrocytomas. It provides three significant benefits:

* It allows your healthcare team to get tissue from the tumor to view it under a microscope to determine the exact type.
* Providers can perform additional tests on the tumor to look for proteins and mutations that certain medications could target.
* It offers the possibility to remove as much of the tumor as possible. This can help relieve pressure and prevent other issues in your brain and skull.

Since grade 1 astrocytomas grow slowly and don’t spread to other areas of your brain, surgery is usually all it takes to treat them.

**Adjuvant therapies for astrocytomas**

Adjuvant therapy, sometimes called helper therapy, targets cancer cells that primary treatment didn’t destroy. In the case of astrocytomas, surgery is the primary treatment.

Grade 3 and grade 4 astrocytomas always require treatments other than surgery alone. Grade 2 astrocytomas may sometimes require adjuvant therapy.

Adjuvant therapies for astrocytomas include:

* **Chemotherapy with temozolomide (TMZ)**: Chemotherapy involves medications that destroy cancer cells and/or prevent them from multiplying. Temozolomide (TMZ) is a drug that works by changing the DNA of tumor cells and, thus, causing the cells to die. TMZ is a first-line adjuvant therapy treatment for every grade 3 and grade 4 astrocytoma. Providers sometimes also prescribe it for grade 2 astrocytomas.
* **Radiation therapy**: This treatment uses radiation (usually high-powered X-rays) to kill cancer cells. It’s typically very effective in helping treat astrocytomas.
* **Bevacizumab**: This is an injected medication that prevents blood vessels from helping the tumor to grow. The U.S. Food and Drug Administration (FDA) has approved bevacizumab for recurrent glioblastomas. It helps reduce swelling and can help improve symptoms.
* **Tumor-treating fields**: This is a special device that produces electrical fields that can delay tumor growth. You wear it like a helmet. Healthcare providers may recommend this treatment for newly diagnosed and recurrent glioblastomas.

**Outlook / Prognosis**

The prognosis (outlook) of astrocytoma depends on several factors, including:

* **Tumor grade**: The prognosis generally gets worse as the grade increases.
* **How much of the tumor can be surgically removed**: While grade 1 astrocytoma is usually cured with surgery alone, it’s impossible to completely remove grade 2 through 4 astrocytomas. However, the more tissue the neurosurgeon can remove, the better the survival rate.
* **Use of adjuvant therapy**: Adjuvant therapy, such as chemotherapy and radiation therapy, can help minimize symptoms and increase the survival rate.
* **Age**: In general, young age is associated with longer survival.
* **Mental status**: Minimal symptoms and normal neurological function are associated with longer survival.

Your healthcare team will be able to give you more accurate information about what you can expect. Don’t be afraid to ask them questions.

**Survival rate of astrocytoma**

The average survival rate varies depending on the grade of astrocytoma:

* **Grade 1 (pilocytic astrocytomas)**: More than 10 years.
* **Grade 2 astrocytomas**: More than five years.
* **Grade 3 astrocytomas:** About two to five years.
* **Grade 4 (glioblastomas)**: About a year.

It’s important to remember that these are just averages based on large groups of people who’ve had astrocytoma. Your healthcare team can provide more detailed information about survival rates based on your unique situation.

**Prevention**

There’s nothing you can do to prevent developing astrocytoma. Most cases happen randomly.

If you have a genetic condition that puts you at higher risk for astrocytoma, be sure to see your healthcare team regularly so they can monitor you for signs of astrocytoma. The earlier they can catch it, the better.

**When should I see my healthcare provider about astrocytoma?**

You may need follow-up appointments with neurologists, oncologists and neurosurgeons to make sure your treatment has worked or is continuing to work.

Contact your healthcare provider as soon as possible if you develop new or worsening symptoms, such as:

* Memory problems.
* Seizures.
* Severe headaches or vision problems.
* Unexplained weight loss.

## 

## **Epidemiology**

### United States statistics

Astrocytoma is the most common brain tumor of childhood. Researchers report that the annual incidence is approximately 14 new cases per million children younger than 15 years.

### Race-, sex-, and age-related demographics

No specific racial predisposition is observed. An analysis of 2000-2017 data from the Surveillance, Epidemiology, and End Results (SEER) Program found that the overall incidence of astrocytomas was lower in Hispanic children than in non-Hispanic White children.

The male-to-female ratio is approximately 1:1, except for supratentorial low-grade gliomas, in which it is approximately 2:1.

Most cases occur in the first decade of life, with the peak incidence occurring in children aged 5-9 years. High-grade supratentorial tumors occur slightly later, with a median age at diagnosis of 9-10 years.

## **Differential Diagnoses**

* Bacterial Meningitis Imaging
* Medulloblastoma Imaging
* Pediatric Aseptic Meningitis
* Pediatric Ependymoma
* Oligodendroglioma
* Meningioma
* Hemangioblastoma
* Pituitary adenoma
* Schwannoma
* Primary CNS lymphoma
* Craniopharyngioma
* Pinealoma (pineal region tumors)
* Arteriovenous malformation (AVM)
* Brain aneurysm
* Bacterial brain abscess
* Tuberculosis (CNS tuberculoma)
* Toxoplasmosis
* Hydatid cyst
* CNS cryptococcosis
* CNS aspergillosis
* Brain metastasis

## **Key Genomic Features:**

* IDH1/IDH2 Mutations:
  + Present in the majority of lower-grade (WHO grade 2 and 3) diffuse astrocytomas and secondary glioblastomas.
  + The most common mutation is IDH1 R132H.
  + IDH mutations occur early in tumor development and produce the oncometabolite 2-hydroxyglutarate, leading to epigenetic changes such as the glioma CpG island methylator phenotype (G-CIMP).
  + IDH-mutant astrocytomas have a better prognosis than IDH-wildtype tumors.
* TP53 Mutations:
  + Frequently co-occur with IDH mutations in diffuse astrocytomas.
  + TP53 is a tumor suppressor gene involved in cell cycle regulation.
* ATRX Mutations:
  + Loss-of-function mutations in ATRX, a chromatin remodeling gene, are common in IDH-mutant astrocytomas.
  + ATRX mutation leads to alternative lengthening of telomeres (ALT), supporting tumor cell immortality.
* CDKN2A Homozygous Deletion:
  + Associated with tumor progression and poorer prognosis.
  + Its presence upgrades IDH-mutant astrocytomas to WHO grade 4 regardless of histology.
* Other Alterations:
  + Amplifications or mutations in PDGFRA, MET, and MYCN are seen especially in higher-grade or progressed tumors.
  + Alterations in DNA repair genes (e.g., MSH2, DNMT3A, RAD51B) can contribute to tumor progression and treatment resistance.
  + Chromosomal rearrangements and deletions increase with tumor grade and progression.
* Molecular Subtypes:
  + IDH-mutant astrocytomas are molecularly distinct from IDH-wildtype glioblastomas.
  + Molecular profiling is now essential for diagnosis and prognosis.

## **Doctor-Patient Conversation: Astrocytoma**

Doctor: Hello, Thank you for coming in today. I have the results from your MRI and the biopsy, and I'd like to discuss them with you. How are you feeling today?

Patient: I'm a bit anxious, doctor. I've been having these headaches and some trouble with my vision. What did the tests show?

Doctor: The tests show that you have a brain tumor called an astrocytoma. This type of tumor arises from star-shaped brain cells called astrocytes. There are different types and grades of astrocytomas, and understanding which kind you have helps us determine the best treatment plan.

Patient: Is it cancer? What does "grade" mean?

Doctor: Yes, astrocytomas are a type of brain cancer. The "grade" refers to how aggressive the tumor is and how quickly it's likely to grow.

* Lower-grade astrocytomas (Grade 1 and 2) are typically slower-growing. A common type in children is a Grade 1 pilocytic astrocytoma, which is often very slow-growing and can sometimes be cured with surgery.
* Higher-grade astrocytomas (Grade 3 anaplastic astrocytoma and Grade 4 glioblastoma) are more aggressive and grow faster. We also look at specific genetic markers, like the IDH mutation status, which helps us further classify the tumor and predict its behavior.

Patient: What are my treatment options?

Doctor: The primary treatment for astrocytoma is surgery to remove as much of the tumor as safely possible. The goal is to reduce symptoms and provide tissue for a definitive diagnosis.

* After surgery, depending on the tumor's grade and if any tumor remains, we often recommend radiation therapy. This uses high-energy beams to kill remaining cancer cells.
* For higher-grade tumors, chemotherapy is usually given in combination with radiation or after radiation. There are different chemotherapy drugs, some given intravenously and others orally.
* For certain genetic profiles, we may also consider targeted therapies that specifically block growth pathways in the tumor cells.

Patient: What are the risks or side effects of these treatments?

Doctor: Each treatment has potential side effects.

* Surgery carries risks like infection, bleeding, and potential neurological changes depending on the tumor's location.
* Radiation can cause fatigue, skin irritation, and temporary hair loss. Over the long term, it can sometimes affect memory or cognition.
* Chemotherapy side effects can include nausea, fatigue, hair loss, and reduced blood counts, increasing the risk of infection.  
  We'll discuss specific risks related to your treatment plan and how we can manage them.

Patient: Will I need lifelong treatment or follow-up?

Doctor: After active treatment, you will need regular follow-up with MRI scans to monitor for any changes or recurrence. The frequency of these scans will depend on your tumor's grade and your overall condition. Many patients also benefit from rehabilitation services, like physical therapy, occupational therapy, or speech therapy, to help regain function.

Patient: What is the prognosis?

Doctor: Prognosis varies greatly depending on the type and grade of astrocytoma, how much of the tumor can be removed, and your overall health. Lower-grade tumors generally have a better prognosis than higher-grade ones. The presence of the IDH mutation is also a positive prognostic factor. We will provide you with a more specific prognosis once we have all the final pathology and genetic reports.

Patient: Thank you, doctor. This is a lot to take in, but I appreciate you explaining it clearly.

Doctor: You're very welcome, Mr. Johnson. It's a lot of information, and it's natural to feel overwhelmed. We have a team of specialists here – neurosurgeons, radiation oncologists, medical oncologists, and supportive care providers – who will work together to develop the best plan for you. We're here to support you every step of the way. Please don't hesitate to ask any questions that come to mind.

**What questions should I ask my doctor?**

It may be helpful to ask your healthcare team the following questions:

**What is the difference between astrocytoma and glioblastoma?**

Glioblastoma is a type of astrocytoma — a grade 4 astrocytoma, specifically. Glioblastoma is an aggressive cancerous tumor that grows and spreads quickly. It’s the most common cancerous primary brain tumor.

**Is astrocytoma malignant or benign?**

There are several types of astrocytoma tumors — some are benign and some are malignant. Grade 1 astrocytomas are benign (noncancerous). Grades 2 through 4 are malignant (cancerous).

## **Why did I get astrocytoma?**

* The exact cause of astrocytoma is not fully understood.
* Many cases appear to be random, but some risk factors include:
  + Genetic predisposition: Certain inherited syndromes like Li-Fraumeni syndrome, neurofibromatosis type 1, tuberous sclerosis, and Turcot syndrome increase risk.
  + Radiation exposure: Prior radiation therapy to the head or neck area significantly increases risk.
  + Age: Risk increases with age, most common between 45 and 65 years.
  + Genetic mutations: Mutations in genes such as IDH1 contribute to tumor development by altering cell metabolism and growth regulation.
* Lifestyle factors have not been clearly linked to astrocytoma risk.

## 2. **What kind of astrocytoma do I have?**

* Astrocytomas are classified by grade (1 to 4) and molecular features:
  + Low-grade (Grade 1-2): Slow-growing, often with IDH1 mutation.
  + High-grade (Grade 3 anaplastic astrocytoma and Grade 4 glioblastoma): More aggressive, may be IDH-wildtype.
* Your doctor will determine the exact type based on biopsy and genetic testing (e.g., IDH mutation status, MGMT methylation).

## 3. **What’s the best treatment for me?**

* Treatment depends on tumor grade, location, size, and molecular markers.
* Common approaches include:
  + Surgery to remove as much tumor as possible.
  + Radiation therapy post-surgery for higher-grade tumors or residual disease.
  + Chemotherapy, often temozolomide, especially for high-grade tumors.
  + Targeted therapies or clinical trials may be options depending on molecular profile.
* Your neuro-oncology team will tailor a plan specific to your tumor and health.

## 5. **What are the treatment risks and side effects?**

* Surgery: Risks include infection, bleeding, neurological deficits depending on tumor location.
* Radiation: Fatigue, skin irritation, hair loss, possible cognitive changes long-term.
* Chemotherapy: Nausea, fatigue, low blood counts, increased infection risk, hair loss.
* Side effects vary by individual and treatment intensity; supportive care helps manage them.

## 6. **What type of follow-up care do I need after treatment?**

* Regular MRI scans to monitor for tumor recurrence or progression.
* Neurological exams and symptom monitoring.
* Management of any long-term side effects, including rehabilitation, hormone replacement if needed, and cognitive support.
* Follow-up frequency depends on tumor grade and treatment response.

## 7. **What are the chances that the cancer will come back or spread after treatment?**

* Recurrence risk varies by tumor grade:
  + Low-grade astrocytomas have a better prognosis but can progress over time.
  + High-grade astrocytomas and glioblastomas have higher recurrence rates and poorer prognosis.
* Spread outside the CNS is rare but possible in advanced disease.

## 8. **What signs of tumor growth should I look for?**

* New or worsening neurological symptoms such as:
  + Headaches, especially worsening or persistent
  + Seizures
  + Weakness or numbness in limbs
  + Changes in vision or speech
  + Cognitive or personality changes
  + Balance or coordination problems
* Report any new symptoms promptly.

## 9. What signs of treatment complications should I look for?

* Signs of infection (fever, chills) due to low blood counts
* Excessive fatigue or bleeding/bruising
* Severe nausea or vomiting
* New neurological deficits or worsening symptoms
* Skin changes or severe reactions at radiation sites
* Any unusual symptoms should be reported immediately.

## 10. Are my family members at risk of developing astrocytoma?

* Most astrocytomas are not inherited and occur sporadically.
* However, if there is a family history of genetic cancer syndromes (e.g., Li-Fraumeni, neurofibromatosis), relatives may have a higher risk.
* Genetic counseling can help assess familial risk if indicated.

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**GLIOBLASTOMA**

A glioblastoma is a fast-growing brain tumor that affects adults.

Glioblastoma (GBM) is the most common type of malignant (cancerous) brain tumor in adults. It starts in a type of glial cell in your brain and spinal cord called astrocytes. Cancer cells rapidly grow and multiply. They can spread into other areas of your brain and spinal cord. Rarely, cancer spreads beyond these areas.

Glial cells, including astrocytes, are vital to help nerve cells function. GBMs are the fastest-growing astrocytoma (a tumor that forms in astrocytes).

Glioblastoma, formerly known as glioblastoma multiforme, is a devastating type of cancer that can result in death in fewer than six months without treatment. More than 13,000 Americans are diagnosed with GBM every year.

If you notice any symptoms like vision changes, memory problems, headaches or seizures, visit a healthcare provider as soon as possible.

**Symptoms and Causes**

Glioblastoma (GBM) is the most common type of malignant (cancerous) brain tumor in adults.

**Symptoms of glioblastoma**

Glioblastoma symptoms may include:

* Blurred or double vision
* Headaches
* Loss of appetite
* Memory problems
* Mood or personality changes
* Muscle weakness or balance issues
* Nausea and vomiting
* Seizures
* Speech problems
* Changes in sensation, numbness or tingling

Glioblastoma symptoms tend to come on quickly. The growing tumor puts pressure on your brain and can destroy healthy brain tissue.

**Glioblastoma causes**

Researchers don’t know the exact cause. Like other gliomas (tumors that form in your brain and spinal cord), researchers suggest that changes in your DNA lead to the development of glioblastoma brain tumors. Your genes contain DNA. They give instructions to your cells about how to grow and multiply. Mutations, or changes, to the DNA in your genes can cause cells to multiply out of control.

**Is glioblastoma hereditary?**

It’s possible to inherit genetic variations from your biological parents. But inherited GBMs are rare. Most commonly, these mutations happen randomly during your lifetime.

**Risk factors of glioblastoma**

Glioblastoma most often affects people ages 45 to 70. The average age at diagnosis is 64.

These factors may increase your risk:

* Exposure to chemicals, like pesticides, petroleum, synthetic rubber and vinyl chloride
* Genetic, tumor-causing conditions, like neurofibromatosis, Li-Fraumeni syndrome and Turcot syndrome
* Previous radiation therapy to your head

**Complications of glioblastoma**

Glioblastoma and its treatments may affect brain function. You could experience mood changes and memory problems. Most people with GBM eventually have to stop working and driving. You may need full-time care. These changes could lead to anxiety disorders or depression.

**Diagnosis and Tests**

A healthcare provider will evaluate your symptoms and perform a neurological exam. If they suspect you may have a brain tumor, you may have these tests:

* MRI or CT scan to look for brain tumors
* Biopsy to get a sample of a tumor and examine the tissue for cancer cells

**Grades of glioblastoma**

Healthcare providers use a grading system from I (1) to IV (4) to indicate brain tumor behavior. Grade I brain tumors grow slowly and are the least aggressive. Grade IV tumors grow rapidly and are more aggressive. Glioblastoma tumors are grade IV.

Glioblastoma can be either primary or secondary:

* **Primary GBM**. It develops directly from glial cells.
* **Secondary GBM**. Grade I glial tumors progress to become GBMs.

**Management and Treatment**

Treatment may include tumor removal surgery (craniotomy), radiation and chemotherapy. If surgery isn’t a safe option, your care team may suggest radiation and chemotherapy to try to manage the tumor.

Glioblastoma treatment options include:

* **Radiation therapy**. Uses X-rays to damage cancer cells. You may need up to 30 daily treatments over six weeks.
* **Intensity-modulated radiation therapy (IMRT)**. Delivers radiation to the tumor while sparing healthy brain tissue.
* **Stereotactic radiosurgery (Gamma Knife)**. Uses focused energy beams to target the tumor with minimal damage to healthy tissue. Often used if GBM returns after IMRT.
* **Chemotherapy**. Circulates medication in your bloodstream to kill cancer cells. Often combined with radiation and continued afterward.
* **Laser interstitial thermal therapy (LITT)**. Uses laser energy to destroy the tumor.
* **Targeted therapy**. Targets certain cell changes that fuel cancer growth. It’s an alternative to chemotherapy.
* **Tumor treatment fields (TTF)**. Sends low-intensity electric fields to the tumor via scalp electrodes that disrupt cancer cell growth. Often used after chemo-radiation.
* **Immunotherapy**. Uses your body’s immune system to fight the GBM cells.
* **Palliative care**. Provides symptom relief and emotional support.

There isn’t a cure for glioblastoma.

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

You should call your healthcare provider if you experience:

* Memory problems
* Seizures
* Severe headaches or vision issues
* Unexplained weight loss or nausea and vomiting
* Change in personality
* Progressively worsening weakness, numbness or speech problems

**Outlook / Prognosis**

Glioblastoma may result in early death shortly after a diagnosis without treatment. But treatments are available. They may help you ease symptoms and stay comfortable or prolong your life.

Clinical trials are underway to find new treatments. And therapies that target specific cancer cell genes show promise. Researchers are also looking at ways to deliver chemotherapy directly to the brain tumor. Your provider will let you know if a clinical trial is right for you.

Most people live an average of 12 to 18 months after diagnosis. The five-year survival rate for glioblastoma is only about 5%. That means about 5% of people with GBM are still alive five years after their diagnosis.

**Prevention**

Genetic mutations that cause glioblastoma aren’t preventable. But early detection and treatment may slow the progression of a tumor.

If brain tumors run in your biological family, you may want to consider genetic testing. Talk to a healthcare provider or a genetic counselor about the risks and benefits of genetic testing.

## **Diagnostic Considerations**

Other conditions to consider in the differential diagnosis of glioblastoma include the following:

* Astrocytoma
* Oligodendroglioma
* Cerebral Metastasis
* Primary CNS lymphoma
* Cerebral abscess
* Cavernous malformation
* Encephalitis
* Intracranial hemorrhage
* Radiation necrosis
* Toxoplasmosis

## 

## **Differential Diagnoses**

* Astrocytoma
* Intracranial Hemorrhage
* Oligodendroglioma
* Primary CNS Lymphoma
* Radiation Necrosis
* Toxoplasmosis

## 

## **Epidemiology**

Glioblastoma is the most frequent malignant brain tumor in adults, accounting for approximately 12-15% of all primary intracranial neoplasms and 45-55% of all gliomas.The overall incidence of glioblastoma varies worldwide and is highest in North America, Australia, and Northern and Western Europe.In the United States, the average annual age-adjusted incidence rate of GBM is 3.19 per 100,000 persons, and the overall prevalence is 9.23 per 100,000 persons.Recent studies have shown that incidence is increasing in England,but there does not appear to be any trend toward increased incidence in the United States or Canada.These discrepancies may be due to differences in genetics or environmental factors, but they are more likely a reflection of international differences in surveillance procedures, reporting practices, and changes in classifications of glioblastoma over time.

In the United States, glioblastoma is 1.59 times more common in males than females, with an annual age-adjusted incidence of 4.03 and 2.54 per 100,000 persons, respectively.With regard to race and ethnicity, incidence is highest among non-Hispanic whites (3.51 per 100,000 persons) and lowest among Asians or Pacific Islanders (1.18 per 100,000 persons).

Glioblastoma may manifest in persons of any age but preferentially affects older adults. The incidence rate increases with age, peaking at 75-79 years, and the median age at diagnosis is 64 years.

Although existing epidemiologic data are based on the previous WHO guidelines, implementation of the 2021 WHO guidelines is unlikely to result in a substantial change in incidence rates, because approximately 90% of all GBMs were *IDH*-wildtype while just 10% were IDH-mutant.However, because IDH-mutant GBM were more common in young people and in women, there will likely be a notable increase in the average age of onset and the incidence for men.

**Recommendations for first-line treatment are as follows:**

* In patients 70 years or younger with good PS (KPS ≥60), regardless of the tumor's *MGMT* methylation status: Fractionated standard brain radiation therapy (RT) plus concurrent and adjuvant temozolomide (TMZ) with or without alternating electric field therapy
* In patients 70 years or younger with poor PS (KPS < 60), regardless of the tumor’s *MGMT* methylation status: Hypofractionated brain RT with or without concurrent or adjuvant TMZ, or TMZ alone, or palliative care alone
* In patients older than 70 years with good PS (KPS ≥60) and *MGMT* promoter–methylated tumors: Hypofractionated brain RT plus concurrent and adjuvant TMZ or standard brain RT plus concurrent and adjuvant TMZ and alternating electric field therapy
* In patients older than 70 years with good PS (KPS ≥60) and *MGMT* unmethylated or indeterminant tumors: Standard brain RT plus concurrent and adjuvant TMZ and alternating electric field therapy
* In patients older than 70 years with poor PS (KPS < 60), regardless of the tumor’s *MGMT* methylation status: Hypofractionated brain RT alone, or TMZ alone, or palliative care alone

**Genomic Data of Glioblastoma (GBM)**:

* IDH Mutation Status:
  + Glioblastomas are classified into two major molecular subtypes based on IDH1 and IDH2 gene mutations.
  + IDH-wildtype GBM accounts for about 90–95% of cases and typically occurs in older adults (>40 years). This subtype has a poor prognosis and aggressive clinical behavior.
  + IDH-mutant GBM (secondary GBM) arises from lower-grade gliomas and is more common in younger patients. It represents about 5–10% of GBM cases and is associated with a better prognosis and longer survival (median survival ~31 months vs. 15 months for wildtype).
  + IDH mutations alter enzyme function, producing the oncometabolite 2-hydroxyglutarate, leading to epigenetic changes and altered metabolism.
* MGMT Promoter Methylation:
  + Methylation of the MGMT (O6-methylguanine-DNA methyltransferase) promoter is a key epigenetic marker influencing response to alkylating chemotherapy (temozolomide).
  + MGMT methylation is more frequent in IDH-mutant tumors but also present in some IDH-wildtype GBMs.
  + Patients with MGMT-methylated tumors generally have better progression-free and overall survival.
* Other Genetic Alterations:
  + Common in IDH-wildtype GBM are amplifications of EGFR, mutations or deletions in PTEN, TP53, TERT promoter mutations, and chromosome 7 gain / chromosome 10 loss.
  + These alterations contribute to tumor growth, invasion, and resistance to therapy.

## **Doctor-Patient Conversation: Glioblastoma**

Doctor: Hello,I have reviewed your MRI and biopsy results, and I’d like to discuss your diagnosis with you. How are you feeling today?

Patient: I’m anxious, doctor. What did the tests show?

Doctor: The tests show that you have a tumor called glioblastoma, which is a type of aggressive brain tumor. It arises from the supportive cells in the brain called astrocytes. Glioblastoma is the most common and malignant form of brain cancer in adults.

Patient: What causes glioblastoma? Is it inherited?

Doctor: The exact cause isn’t fully understood. Most cases happen randomly and are not inherited. Some risk factors include exposure to high doses of radiation and certain rare genetic syndromes, but most patients don’t have a clear risk factor.

Patient: What treatment options do I have?

Doctor: Treatment usually involves several steps:

* Surgery to remove as much of the tumor as safely possible.
* Radiation therapy to target remaining tumor cells.
* Chemotherapy, typically with a drug called temozolomide, which is given alongside radiation and then as maintenance therapy.
* We will also look at molecular markers in your tumor to tailor treatment and consider clinical trials if appropriate.

Patient: What are the side effects of these treatments?

Doctor: Surgery risks depend on tumor location but can include neurological changes. Radiation can cause fatigue, skin irritation, and sometimes cognitive changes. Chemotherapy side effects may include nausea, fatigue, and low blood counts. We will provide supportive care to manage side effects.

Patient: What is my prognosis?

Doctor: Glioblastoma is an aggressive tumor, and despite treatment, it is challenging to cure. The average survival is about 15 months, but this varies widely depending on factors like your age, overall health, and specific tumor genetics. Some patients respond better to treatment and live longer.

Patient: Will I need follow-up after treatment?

Doctor: Yes, you will have regular MRI scans to monitor for tumor recurrence and ongoing assessments to manage any side effects or neurological symptoms. Supportive care, rehabilitation, and counseling are important parts of your care.

Patient: Are there any new treatments or clinical trials I should know about?

Doctor: There are ongoing clinical trials exploring new therapies like immunotherapy and targeted treatments. We can discuss whether you are eligible for any trials that might be suitable.

Patient: Thank you, doctor. This is a lot to take in, but I appreciate your honesty.

Doctor: I understand this is overwhelming. We have a multidisciplinary team here to support you through every step. Please feel free to ask any questions anytime.

**Glioblastoma Procedure and Treatment Timeline**

## 1. Diagnosis and Initial Evaluation

* Neurological exam and MRI to identify tumor location and size.
* Biopsy or surgical resection to obtain tissue for diagnosis and molecular testing.
* Timeline: Usually completed within days to 1–2 weeks after symptom onset.

## 2. Surgery

* Goal: Maximal safe resection of the tumor to reduce tumor burden and improve symptoms.
* Procedure: Craniotomy (open skull surgery), sometimes awake surgery if tumor is near critical brain areas.
* Limitations: GBM is diffuse; complete removal is usually impossible due to infiltration into healthy brain tissue.
* Timeline: Surgery scheduled promptly after diagnosis, often within 1–3 weeks.

## 3. Postoperative Recovery

* Healing of surgical site typically takes 2–4 weeks before starting further treatment.
* Early postoperative MRI within 24–72 hours to assess extent of resection.

## 4. Radiation Therapy + Concurrent Chemotherapy (Stupp Protocol)

* Begins approximately 4 weeks after surgery to allow wound healing.
* External beam radiation therapy (EBRT): Daily sessions, 5 days a week for about 6 weeks (total ~30 sessions).
* Concurrent chemotherapy: Oral temozolomide (TMZ) given daily during radiation.
* This combined approach improves median survival compared to radiation alone.

## 5. Adjuvant Chemotherapy

* After completion of radiation, patients receive adjuvant temozolomide for 6 months (typically 5 days per 28-day cycle).
* This phase targets residual tumor cells and helps delay progression.

## 6. Follow-Up and Monitoring

* Regular clinical evaluations and MRI scans every 2–3 months to detect recurrence or progression.
* Supportive care and symptom management throughout.

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**MENINGIOMA**

**DEFINITION AND DESCRIPTION**

A meningioma is a tumor that grows from the membranes that surround the brain and spinal cord, called the meninges. A meningioma is not a brain tumor, but it may press on the nearby brain, nerves and vessels. Meningioma is the most common type of tumor that forms in the head.

Most meningiomas grow very slowly. They can grow over many years without causing symptoms. But sometimes, their effects on nearby brain tissue, nerves or vessels may cause serious disability.

Meningiomas occur more often in women. They're often found at older ages. But they can happen at any age.

Because most meningiomas grow slowly, often without symptoms, they do not always need treatment right away. Instead, they may be watched over time.

**Symptoms**

Symptoms of a meningioma most often begin slowly. They may be hard to notice at first. Symptoms may depend on where in the brain the meningioma is. Rarely, it can be in the spine.

Symptoms may include:

* Changes in vision, such as seeing double or blurring.
* Headaches that are worse in the morning.
* Hearing loss or ringing in the ears.
* Memory loss.
* Loss of smell.
* Seizures.
* Weakness in the arms or legs.
* Trouble speaking.

**When to see a doctor**

Most symptoms of a meningioma come on slowly. But sometimes a meningioma needs care right away.

**Seek emergency care** if you have:

* Sudden onset of seizures.
* Sudden changes in vision or memory.

**Make an appointment to see your healthcare professional** if you have lasting symptoms that worry you, such as headaches that get worse over time.

Often, because meningiomas do not cause any symptoms you notice, they are found only from imaging scans done for other reasons.

**Causes**

It isn't clear what causes a meningioma. Experts know that something changes some cells in the meninges. The changes makes them multiply out of control. This leads to a meningioma.

Being exposed to radiation as a child is the only known environmental risk factor for getting meningioma. There's no good evidence to show that meningiomas happen because of cellphone use.

**Risk factors**

Risk factors for a meningioma include:

* **Radiation treatment.** Radiation therapy that involves the head may increase the risk of a meningioma.
* **Female hormones.** Meningiomas are more common in women. This might mean that female hormones may play a role. Some studies also have suggested a link between breast cancer and meningioma risk related to the role of hormones. Some research suggests that the use of oral birth control and hormone replacement therapy could raise the risk of meningioma growth.
* **An inherited nervous system condition.** The rare condition neurofibromatosis 2 increases the risk of meningioma and other brain tumors.
* **Obesity.** A high body mass index (BMI) is a risk factor for many types of cancers. Several large studies have found that meningiomas happen more often in obese people. But the link between obesity and meningiomas is not clear.

**Complications**

A meningioma and its treatment can cause long-term complications. Treatment most often involves surgery and radiation therapy. Complications may include:

* Trouble focusing.
* Memory loss.
* Personality changes.
* Seizures.
* Weakness.
* Changes in the senses.
* Trouble with language.

Your healthcare professional can treat some complications and refer you to specialists to help you cope with other complications.

**DIAGNOSIS**

A meningioma can be hard to diagnose because the tumor is often slow growing. Symptoms of a meningioma also may be subtle and thought to be other health conditions or signs of aging.

If your healthcare professional suspects a meningioma, you may be referred to a doctor who specializes in conditions of the brain and spine, called a neurologist.

To diagnose a meningioma, a neurologist conducts a thorough neurological exam followed by an imaging test with contrast dye, such as:

* **CT scan.** CT scans take X-rays that make cross-sectional images of a full picture of the brain. Sometimes an iodine-based dye is used to make the picture easier to read.
* **MRI scan.** With this imaging study, a magnetic field and radio waves create cross-sectional images of the structures in the brain. MRI scans provide a more detailed picture of the brain and meningiomas.

Sometimes, a sample of the tumor sent to a lab for study, called a biopsy, may be needed to rule out other types of tumors and confirm a meningioma diagnosis.

**Treatment**

Treatment for a meningioma depends on many factors, including:

* The size of the meningioma and where it is.
* The rate of growth of the tumor.
* Your age and overall health.
* Your goals for treatment.

**Wait-and-see approach**

Not everyone with a meningioma needs treatment right away. A small, slow-growing meningioma that isn't causing symptoms may not need treatment.

If the plan is for you not to have treatment for a meningioma, you'll likely have brain scans at times to assess your meningioma and look for signs that it's growing.

If your healthcare provider finds that the meningioma is growing and needs to be treated, you have several treatment choices.

**Surgery**

If the meningioma causes symptoms or shows signs that it's growing, your healthcare professional may suggest surgery.

Surgeons work to remove the entire meningioma. But because a meningioma may be near fragile structures in the brain or spinal cord, it isn't always possible to remove the entire tumor. Then, surgeons remove as much of the meningioma as they can.

The type of treatment, if any, you need after surgery depends on several factors.

* **If no visible tumor remains,** then no further treatment may be needed. But you will have follow-up scans from time to time.
* **If the tumor is benign and only a small piece remains,** then your healthcare professional may suggest follow-up scans only. Some small leftover tumors may be treated with a form of radiation treatment called stereotactic radiosurgery.
* **If the tumor is irregular or cancer,** you'll likely need radiation.

Surgery may pose risks including infection and bleeding. The risks of your surgery will depend on where your meningioma is. For instance, surgery to remove a meningioma from around the optic nerve can lead to vision loss. Ask your surgeon about the risks of your surgery.

**Radiation therapy**

If the entire meningioma can't be removed surgically, your healthcare professional may suggest radiation therapy after or instead of surgery.

The goal of radiation therapy is to destroy any meningioma cells that are left and reduce the chance that the meningioma may come back. Radiation therapy uses a large machine to aim high-powered energy beams at the tumor cells.

Advances in radiation therapy increase the dose of radiation to the meningioma while giving less radiation to healthy tissue. Radiation therapy types for meningiomas include:

* **Stereotactic radiosurgery (SRS).** This type of radiation treatment aims at several beams of powerful radiation at a precise point. Despite its name, radiosurgery doesn't involve scalpels or cuts. Radiosurgery most often is done in an outpatient setting in a few hours. Radiosurgery may be a choice for people with meningiomas that can't be removed with conventional surgery or for meningiomas that come back despite treatment.
* **Fractionated stereotactic radiotherapy (SRT).** This type gives radiation in small fractions over time, such as one treatment a day for 30 days. This approach may be used for tumors too large for radiosurgery or those in an area where radiosurgery is too strong, such as near the optic nerve.
* **Intensity-modulated radiation therapy (IMRT).** This uses computer software to lower the intensity of radiation to the meningioma site. This may be used for meningiomas that are near sensitive brain structures or those with a complex shape.
* **Proton beam radiation.** This uses radioactive protons aimed right at the tumor. This type lessens damage to the tissue around the tumor.

**Medicines**

Medicine therapy, also called chemotherapy, rarely is used to treat meningiomas. But it may be used when the meningioma doesn't respond to surgery and radiation.

There isn't a widely used chemotherapy approach to the treatment of meningiomas. But researchers are studying other targeted approaches.

**Alternative medicine**

Alternative medicine treatments don't treat meningioma. But some may help give relief from treatment side effects. Or they might help you cope with the stress of having a meningioma.

Alternative medicine therapies that may be helpful include:

* Acupuncture.
* Hypnosis.
* Massage.
* Meditation.
* Music therapy.
* Relaxation exercises.

Discuss choices with your healthcare professional.

**DIFFERENTIAL DIAGNOSIS**

* Oligodendroglioma
* Astrocytoma
* Hemangioblastoma
* Pituitary adenoma
* Schwannoma
* Primary CNS lymphoma
* Medulloblastoma
* Ependymoma
* Craniopharyngioma
* Pinealoma (pineal region tumors)
* Arteriovenous malformation (AVM)
* Brain aneurysm
* Bacterial brain abscess
* Tuberculosis (CNS tuberculoma)
* Toxoplasmosis
* Hydatid cyst
* CNS cryptococcosis
* CNS aspergillosis
* Brain metastasis
* Dural metastases (can mimic en plaque meningiomas)
* Hemangiopericytoma (solitary fibrous tumor)
* Lymphoma involving dura
* Meningothelial hyperplasia (benign proliferation mimicking meningioma)

**Epidemiology of Meningioma**

* Prevalence and Incidence:
  + Meningioma is the most common primary brain tumor, accounting for about 36% of all primary central nervous system tumors in the United States.
  + The prevalence of pathologically confirmed meningioma is approximately 97.5 cases per 100,000 individuals in the U.S., with over 170,000 people currently diagnosed.
  + The annual incidence rate is about 7.6 to 8.8 per 100,000 persons, varying slightly by study and population.
* Age Distribution:
  + Meningiomas can occur at any age but are most frequently diagnosed in middle-aged and older adults, especially those aged 40 to 60 years and above.
  + The risk increases with age in both men and women.
  + In children and adolescents, meningiomas are rare, accounting for about 1.5% of brain tumors.
* Sex Differences:
  + Women are affected approximately twice as often as men (female-to-male ratio ~2:1).
  + The incidence rate in females is around 8.36 per 100,000, compared to 3.61 per 100,000 in males.
  + This female predominance is thought to be related to hormonal influences.
  + In rare cases of pre-pubertal meningiomas, this ratio may be reversed (more common in males).
  + Atypical and malignant meningiomas (~5% of cases) show a slight male predominance.
* Race and Ethnicity:
  + Meningiomas are more commonly diagnosed in Black non-Hispanic individuals compared to White non-Hispanic and Hispanic populations.
  + Reported incidence rates are approximately 6.67 per 100,000 in Black non-Hispanics versus about 5.9 per 100,000 in Whites and Hispanics.
* Trends Over Time:
  + Incidence of non-malignant meningiomas has increased over recent decades, likely due to improved imaging and diagnosis.
  + Malignant meningioma incidence has remained low and stable or slightly decreased.
* Risk Factors:
  + Ionizing radiation exposure is a known risk factor but accounts for few cases overall.
  + Increased body mass index (BMI) is associated with higher risk.
  + A history of allergies or atopic diseases appears protective.
  + Genetic factors, including variants in genes like MLLT10 and RIC8A, have been identified as low-penetrance risk alleles.

**Genomic Data of Meningioma**

## 1. NF2 Gene Mutations and Chromosome 22 Loss

* The NF2 gene on chromosome 22q12.2 is the most commonly altered gene in meningiomas, mutated or inactivated in approximately 40–60% of sporadic meningiomas.
* NF2 encodes the tumor suppressor protein Merlin, and its loss is a critical early event in meningioma tumorigenesis.
* NF2 mutations and chromosome 22 monosomy are more frequent in high-grade meningiomas (about 80%) compared to low-grade tumors (~43%).
* NF2 alterations are associated with tumors arising from the cerebral and cerebellar convexities.

## 2. Non-NF2 Driver Mutations

* Several other recurrent somatic mutations are found in about 40% of sporadic meningiomas, often mutually exclusive with NF2 mutations. These include:
  + TRAF7 (TNF receptor-associated factor 7), involved in pro-apoptotic signaling.
  + KLF4 (Kruppel-like factor 4), a pluripotency transcription factor.
  + AKT1 (v-Akt murine thymoma viral oncogene homolog 1), an oncogene activating PI3K/AKT pathway.
  + SMO (Smoothened), a Hedgehog pathway signaling member.
  + PIK3CA, another oncogene in the PI3K pathway.
* These mutations are more common in low-grade meningiomas and tend to occur without concurrent NF2 alterations.

## 3. Genomic Differences Between Low- and High-Grade Meningiomas

* High-grade meningiomas show significantly higher rates of chromosomal gains and losses, especially monosomy 22.
* Non-NF2 driver mutations (TRAF7, KLF4, AKT1, SMO) are significantly less frequent in high-grade meningiomas.
* This suggests that high-grade tumors may arise through different molecular pathways, often dominated by NF2 loss.

## **Doctor-Patient Conversation: Meningioma**

Doctor: Hello, I want to discuss the results of your MRI and what we know about the meningioma found in your brain. How are you feeling today?

Patient: I’m a bit worried, doctor. What exactly is a meningioma?

Doctor: A meningioma is a tumor that arises from the meninges, which are the membranes covering your brain and spinal cord. Most meningiomas are benign, meaning they are not cancerous, and they often grow slowly. However, depending on their size and location, they can cause symptoms by pressing on nearby brain tissue.

Patient: Is my tumor dangerous? How big is it? Is it growing?

Doctor: Your tumor is currently small and appears to be growing very slowly, if at all. We will monitor it closely with regular MRI scans to see if it changes over time. Many meningiomas remain stable for years without causing problems.

Patient: Do I need treatment now? What are my options?

Doctor: Because your meningioma is small and not causing significant symptoms, the best approach right now is active surveillance — that means regular MRI scans and clinical check-ups. If it grows or starts causing symptoms, we can consider treatment options such as surgery or radiation therapy. Surgery aims to remove the tumor, and radiation can help control growth if surgery isn’t suitable.

Patient: What are the risks of surgery or radiation?

Doctor: Surgery carries risks like any operation, including infection, bleeding, or neurological changes depending on the tumor’s location. Radiation therapy can cause fatigue, skin irritation, and sometimes longer-term effects on brain function. We carefully weigh these risks against the benefits before recommending treatment.

Patient: What symptoms should I watch for that might mean the tumor is growing?

Doctor: New or worsening headaches, seizures, changes in vision or hearing, weakness or numbness on one side of the body, or cognitive changes should prompt you to contact us promptly. Early detection of changes helps us intervene sooner.

Patient: Will this affect my daily life or activities?

Doctor: Many people with meningiomas live normal lives, especially when the tumor is small and stable. Some patients do experience fatigue or cognitive difficulties even after treatment, so we provide supportive care and rehabilitation if needed.

Patient: Should I get a second opinion?

Doctor: If it would make you feel more comfortable, we can arrange that. Many patients find second opinions helpful, especially when deciding on treatment.

Patient: Thank you, doctor. This helps me understand what to expect.

Doctor: You’re welcome. We’ll work together to monitor your meningioma and support you every step of the way. Please don’t hesitate to reach out with any concerns or questions.

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**OVARIAN GERM CELL TUMORS**

**DEFINITION AND DESCRIPTION**

Ovarian germ cell tumors develop from reproductive cells (germ cells) inside your ovaries. Ovaries are two small pelvic organs that play an important role in the female reproductive system. They produce eggs during your reproductive years. The germ cells inside your ovaries eventually mature (“germ”-inate) into eggs. With ovarian germ cell tumors, some of these cells clump together to form an abnormal mass instead.

Ovarian germ cell tumors usually form in just one ovary, but sometimes they appear in both.

Most ovarian germ cell tumors are benign (noncancerous). Rarely, they can be malignant (cancerous). These tumors can spread and damage healthy tissue. Malignant germ cell tumors are a rare form of ovarian cancer.

**Types of ovarian germ cell tumors**

The most common types of ovarian germ cell tumors are:

* **Mature teratoma (dermoid cyst)**: These benign tumors are the most common type of ovarian germ cell tumor. Most people diagnosed are in their teens, 20s or 30s.
* **Dysgerminoma**: This is the most common type of malignant ovarian germ cell tumor. But most of these tumors (70% of diagnoses) aren’t considered aggressive (fast-spreading) and respond well to treatment. Most people diagnosed are in their 20s or 30s.
* **Immature teratoma**: This is a fast-growing malignant tumor that can spread from your ovary to other parts of your body (metastasis). It’s most common in people 20 years old and younger.
* **Yolk sac tumors (endodermal sinus tumors)**: These malignant tumors grow quickly and spread fast. They’re most common in people 20 years old and younger. Up to 40% of diagnoses involve children who are too young to have started their periods.
* **Mixed germ cell tumors**: These malignant tumors contain a mix of other tumor types, usually dysgerminoma and yolk sac tumors.

Rarer ovarian germ cell tumors include:

* Embryonal carcinoma.
* Choriocarcinoma.
* Polyembryoma.

Ovarian germ cell tumors are most common in females in their reproductive years or younger. They account for up to 70% of ovarian growths in people between 10 to 30 years old. They’re less common in people over 40.

Approximately 95% of ovarian germ cell tumors are benign (mature teratomas). Only 2% to 3% of ovarian cancers are germ cell tumors.

**Symptoms and Causes**

It may be difficult to spot signs of ovarian germ cell tumors early on. Benign tumors may not cause symptoms unless they’re large. Symptoms of malignant tumors may not appear until the cancer has advanced.

Symptoms to look out for include:

* Abdominal pain, discomfort or tenderness. (This may start suddenly and be severe.)
* Bloated belly, with or without weight gain in other parts of your body.
* Changes in bowel habits, such as diarrhea or constipation.
* Changes in your eating habits, like loss of appetite.
* Irregular vaginal bleeding, such as bleeding when you’re not on your period or after menopause.

These tumors can release hormones that can cause changes in your body, including symptoms of:

* Early pregnancy, like fatigue, nausea or breast tenderness.
* Early puberty, although this is rare.

**What causes ovarian germ cell tumors?**

Ovarian germ cell tumors form when sex cells (germ cells) undergo changes (mutations) and form a mass. Experts continue to research why this happens, including who’s most likely to develop them.

Although anyone with ovaries can develop these tumors, ovarian germ cell tumors are much more common among people in their reproductive years and younger.

**Complications of ovarian germ cell tumors**

Treatment is important because even if a tumor is benign, it can potentially burst open (rupture) or twist (ovarian torsion). This is more likely to happen if a tumor is large.

Removing the tumor can keep this from happening.

**Diagnosis and Tests**

After asking about your symptoms, your provider will perform several tests, including a pelvic exam to check for growths and other abnormalities in your abdomen, pelvis and vagina. You may also need imaging and blood tests.

* **Imaging tests**: A [t](https://my.clevelandclinic.org/health/diagnostics/4993-transvaginal-ultrasound)ransvaginal ultrasound is often the first imaging test providers perform if they suspect an ovarian germ cell tumor. This test allows your provider to see inside your abdomen and check for growths. You may also need a computed tomography (CT) scan or magnetic resonance imaging (MRI) as part of your diagnosis. These tests can show more detail than an ultrasound.
* **Blood tests**: You may need a serum tumor marker test, a blood test that checks the levels of certain substances in your body. High levels of alpha-fetoprotein (AFP), lactate dehydrogenase (LDH) or human chorionic gonadotropin (HCG) can be signs of ovarian germ cell tumors.

Your provider will need to remove the tumor or the entire affected ovary to make a definitive diagnosis. A pathologist will test the cells in a lab to determine the type of tumor and whether it’s benign or malignant.

**Stages of malignant ovarian germ cell tumors**

If a tumor is malignant, providers classify the cancer using a process called staging as part of your diagnosis. They use imaging procedures, like a CT scan or PET scan (positron emission tomography scan), to measure the tumor size and determine its location. This information helps your provider determine what treatments you’ll need and the likely outcomes of treatment.

Usually, the lower the stage, the more treatable the cancer is.

Stages for malignant ovarian germ cell tumors are:

* **Stage 1**: The cancer is just in your ovaries.
* **Stage 2**: The cancer has spread to other tissues in your pelvis, including your fallopian tubes or uterus.
* **Stage 3**: The cancer has spread to your lymph nodes or the tissue lining your pelvic organs or abdominal cavity (peritoneum), but it hasn’t spread beyond your abdomen.
* **Stage 4 (metastatic cancer)**: The cancer has grown into your liver or spleen or spread to tissues and organs outside your abdomen, like your lungs.

**Management and Treatment**

Most germ cell tumors are treatable. Your treatment plan will depend on the tumor’s size and whether it’s benign or malignant.

Regardless, your provider will take care to conserve as much of your ovary as possible to preserve your fertility if you’re in your reproductive years.

**Benign (noncancerous) ovarian germ cell tumors**

Healthcare providers remove benign tumors surgically. Sometimes, they need to remove the entire ovary (oophorectomy) or part of the ovary (ovarian cystectomy) to get rid of the growth. They may recommend open surgery (laparotomy) or a less invasive type of surgery that involves smaller incisions (laparoscopy).

Benign tumors rarely grow back after providers remove them.

**Malignant (cancerous) ovarian germ cell tumors**

Treatment depends on the type of tumor and the cancer stage. Common treatments include:

* **Surgery**: Your provider may recommend an oophorectomy to remove one or both of your ovaries or fallopian tubes. If cancer has spread beyond your ovaries and fallopian tubes, you may need a total hysterectomy to remove your uterus and cervix.
* **Chemotherapy**: During chemotherapy, your provider delivers medicine into your veins, usually through an infusion. Chemotherapy drugs kill cancerous cells and stop them from multiplying. You may receive chemo treatments over several weeks or months.

**Outlook / Prognosis**

The outlook for benign ovarian germ cell tumors is excellent. Benign tumors usually don’t grow back after providers remove them.

The outlook for malignant germ cell tumors varies depending on the tumor type and cancer stage. Cancer specialists determine outlook by calculating how many people with a specific cancer are alive five years after their diagnosis, or the five-year survival rate.

If cancer hasn’t spread beyond your ovaries, there is a 94% to 98% survival rate. Cancers that have spread farther away from the original tumor site have a 73% five-year survival rate. Your provider will monitor you closely during this period to ensure you receive treatment if the cancer returns (recurs).

**Is ovarian germ cell cancer curable?**

It can be, depending on the type of tumor and the stage. For example, the cure rate for early-stage dysgerminoma treated with chemotherapy is nearly 100%. More aggressive types, like yolk sac tumors, aren’t curable, but treatment can slow tumor growth and cancer spread.

Your provider can explain the prognosis for ovarian germ cell cancer (including the possibility of a cure) based on your diagnosis.

**Prevention**

You can’t prevent germ cell tumors. But you can get regular checkups so your provider can monitor your health and assess your cancer risk.

**When should I see my healthcare provider about ovarian germ cell tumors?**

See a provider immediately if you or your child experiences symptoms of an ovarian germ cell tumor. Some germ cell tumors grow quickly. Finding them early and getting treatment as soon as possible can improve the outlook significantly.

## **Differential Diagnosis of Ovarian Germ Cell Tumors (OGCTs)**

## 1. Types of Ovarian Germ Cell Tumors

OGCTs arise from primitive germ cells of the ovary and include both benign and malignant types. The main tumor types to consider are:

* Dysgerminoma (most common malignant OGCT)
* Immature teratoma
* Yolk sac tumor (endodermal sinus tumor)
* Embryonal carcinoma
* Choriocarcinoma (pure or part of mixed tumors)
* Mixed germ cell tumors (contain two or more germ cell tumor types)
* Mature cystic teratoma (dermoid cyst) (benign)
* Monodermal teratomas (e.g., malignant struma ovarii, carcinoid tumors)

## 2. Other Ovarian Masses to Differentiate From OGCTs

OGCTs must be distinguished from other ovarian and pelvic masses, including:

* Ovarian epithelial tumors (serous, mucinous cystadenomas/carcinomas)
* Ovarian sex cord-stromal tumors (granulosa cell tumor, Sertoli-Leydig cell tumor)
* Tubo-ovarian abscess (infectious/inflammatory mass)
* Stein-Leventhal syndrome (Polycystic ovary syndrome)
* Tubal (ectopic) pregnancy
* Other benign ovarian cysts (functional cysts, endometriomas)

**Ovarian Germ Cell Tumors (OGCTs): Procedures and Treatment Timelines**

## 1. Initial Diagnosis and Surgical Management

* Surgery is the first and most important step.
* For early-stage tumors (Stage I), the usual procedure is unilateral salpingo-oophorectomy (removal of the affected ovary and fallopian tube), preserving the uterus and contralateral ovary to maintain fertility whenever possible.
* Surgical staging includes peritoneal washing, omental biopsy, and selective lymph node sampling if indicated.
* Surgery is typically scheduled soon after diagnosis, often within days to a few weeks depending on patient condition and logistics.

## 2. Postoperative Evaluation and Staging

* Pathology and staging results guide further treatment decisions.
* Patients with completely staged, low-risk Stage IA dysgerminomas may be observed without immediate adjuvant therapy.
* Incompletely staged or higher-stage tumors usually require additional treatment.

## 3. Adjuvant Treatment

* Chemotherapy is the main adjuvant treatment, especially for higher-stage or non-dysgerminoma tumors.
* The standard regimen is BEP chemotherapy (bleomycin, etoposide, cisplatin), given in 3 to 4 cycles.
* Chemotherapy typically starts 3–6 weeks after surgery to allow recovery.
* For bulky or advanced disease, chemotherapy may be given before surgery (neoadjuvant) or intensified with regimens like POMB/ACE.
* Radiation therapy is rarely used due to fertility concerns and limited efficacy.

## 4. Treatment of Advanced or Recurrent Disease

* For Stage III/IV disease, surgery may be more extensive (e.g., total abdominal hysterectomy and bilateral salpingo-oophorectomy) if fertility preservation is not a priority.
* Combination chemotherapy remains the cornerstone, often with more cycles or intensified regimens.
* Salvage chemotherapy, high-dose chemotherapy with stem cell rescue, or clinical trials may be considered for recurrent or refractory tumors.
* Secondary cytoreductive surgery may be considered selectively.

## 5. Follow-Up Care

* After completion of treatment, patients undergo regular follow-up with physical exams, tumor markers (AFP, β-hCG, LDH), and imaging to monitor for recurrence.
* Follow-up frequency is typically every 3 months for the first 2 years, then less frequently.
* Fertility counseling and supportive care are integral parts of follow-up.

**Genomic Data of Ovarian Germ Cell Tumors (OGCTs):**

* Low Mutation Burden and Chromosomal Aberrations:  
  OGCTs generally exhibit a low somatic mutation rate but show frequent chromosomal copy number alterations, especially gains and losses of whole chromosomes or chromosome arms.
* Chromosomal Gains and Losses:
  + The most common chromosomal gain in malignant OGCTs is 12p amplification, particularly in dysgerminomas and yolk sac tumors, similar to testicular germ cell tumors (TGCTs).
  + Other frequent gains include chromosomes 1p, 6p, 12q, 15q, 20q, 21q, and 22q.
  + Common losses involve chromosome 13q.
  + Immature teratomas typically lack 12p gain and have fewer chromosomal changes, suggesting distinct pathogenetic mechanisms.
* Key Mutated Genes:
  + KIT mutations, especially in exon 17, are frequent in dysgerminomas, gonadoblastoma, and yolk sac tumors, leading to increased proliferation of undifferentiated germ cells.
  + Other recurrently altered genes include TP53, KRAS, KMT2D, PIK3CD, and PIK3CA.
  + However, TP53 mutations are rare in yolk sac tumors, contrasting with many other cancers.
  + Mutations in RB1 have been reported in rare mixed germ cell tumors, potentially predisposing to tumor development and progression.
* Genomic Distinctions Among Subtypes:
  + Dysgerminomas and yolk sac tumors share genetic pathways with testicular GCTs, including 12p gains and KIT mutations.
  + Immature teratomas show distinct genomic profiles with near-diploid genomes, severe loss of heterozygosity, and lack of typical oncogenic mutations.
  + Bilateral teratomas arise independently, indicating multiple meiotic errors.
* Molecular Pathways:
  + Aberrations in signaling pathways such as WNT/β-catenin and TGF-β/BMP have been implicated, especially in yolk sac tumors.
  + OGCTs resemble primordial germ cells and pluripotent stem cells, explaining their early onset and histologic complexity.

**Epidemiology of Ovarian Germ Cell Tumors (OGCTs):**

Incidence:

OGCTs are rare ovarian tumors primarily affecting girls, adolescents, and young women.

Incidence rates vary by age and geography but are generally highest in the 10–19-year age group.

Global incidence in girls aged 0–9 years ranges from 0.6 to 2.1 cases per million; incidence increases in adolescents and young adults, reaching up to 27 cases per million in women aged 15–19 years.

In the U.S., malignant OGCTs have an age-adjusted incidence rate of approximately 0.3 to 0.4 per 100,000 women-years.

Age Distribution:

Most common in females aged 10 to 30 years, with a peak incidence in the second and third decades of life.

Rare in children under 10 but can occur.

OGCTs account for about 20% of all ovarian tumors in this young age group but only 3–5% of ovarian malignancies overall.

Geographic Variation:

Higher incidence rates reported in Eastern Asia, Central America, and North America.

Some regions show increasing trends in incidence over recent decades, particularly in areas with high human development indices.

Histologic Subtypes:

Dysgerminomas constitute about 28–33% of malignant OGCTs.

Immature teratomas and mixed germ cell tumors make up the majority of the remainder.

Mature cystic teratomas (benign) are the most common OGCT subtype overall.

Survival:

Overall 5-year survival rates exceed 80% with modern treatment, but survival varies by tumor subtype, stage, and patient age.

## **Doctor-Patient Conversation: Ovarian Germ Cell Tumors**

Doctor: Hello, I want to talk with you about your diagnosis of an ovarian germ cell tumor. How are you feeling today?

Patient: I’m quite anxious, doctor. What exactly is an ovarian germ cell tumor?

Doctor: Ovarian germ cell tumors arise from the cells in your ovary that are meant to develop into eggs. They are relatively rare and mostly affect young women and teenagers. These tumors can be benign or malignant, but the good news is that many types respond very well to treatment.

Patient: What treatment will I need?

Doctor: The first step is usually surgery to remove the tumor. Whenever possible, we try to preserve your fertility by removing only the affected ovary and fallopian tube, keeping the uterus and the other ovary intact. After surgery, depending on the tumor type and stage, you may need chemotherapy to destroy any remaining cancer cells.

Patient: What kind of chemotherapy? Will it affect my fertility?

Doctor: The standard chemotherapy regimen is a combination of drugs called bleomycin, etoposide, and cisplatin, usually given over 3 to 4 cycles. The good news is that most women regain normal menstrual cycles and fertility after treatment, but we will discuss fertility preservation options with you before starting therapy.

Patient: Are there side effects I should be worried about?

Doctor: Chemotherapy can cause side effects like fatigue, nausea, hair loss, and increased risk of infection. We have effective ways to manage these symptoms, and your care team will support you throughout treatment. Surgery also carries risks, but we take every precaution to minimize them.

Patient: What about follow-up? Will I need more tests?

Doctor: Yes, after treatment, you will have regular follow-up visits with physical exams, blood tests for tumor markers like AFP and beta-hCG, and imaging studies to monitor for any recurrence. These visits are usually every few months initially.

Patient: What if the tumor comes back?

Doctor: If the tumor recurs, we have additional chemotherapy options and sometimes surgery to manage it. Clinical trials are also available for new treatments, and we can discuss if you’re eligible.

Patient: Can I participate in clinical trials?

Doctor: Absolutely. Clinical trials are important for advancing treatment and may provide access to newer therapies. We will review ongoing trials suitable for your tumor type and stage.

Patient: Thank you, doctor. This helps me understand what to expect.

Doctor: You’re welcome. We have a multidisciplinary team—including surgeons, oncologists, nurses, and fertility specialists—to support you every step of the way. Please feel free to ask any questions at any time.

**What questions should I ask my healthcare provider?**

## Is the tumor benign or malignant?

* Approximately 95% of ovarian germ cell tumors are benign, most commonly mature cystic teratomas (dermoid cysts).
* About 5% are malignant, including types like dysgerminoma, immature teratoma, yolk sac tumor, embryonal carcinoma, and mixed germ cell tumors.
* Your doctor will determine this based on imaging, tumor markers, and pathology after surgery.

## 2. What tests will I need to determine what treatments I’ll need?

* Imaging: Pelvic ultrasound, CT, or MRI to assess tumor size, location, and spread.
* Serum tumor markers:
  + AFP (alpha-fetoprotein): Elevated in yolk sac tumors, immature teratomas, and some mixed tumors.
  + β-hCG (beta-human chorionic gonadotropin): Elevated in choriocarcinoma and some dysgerminomas.
  + LDH (lactate dehydrogenase): Often elevated in dysgerminomas.
* Surgical biopsy or removal: Pathological examination confirms tumor type and malignancy.
* These tests guide staging and treatment planning.

## 3. What treatments would you recommend?

* Surgery: Usually the first step, aiming to remove the tumor while preserving fertility if possible. Typically, this involves removal of the affected ovary and fallopian tube (unilateral salpingo-oophorectomy).
* Chemotherapy: Recommended for malignant tumors, especially dysgerminomas, yolk sac tumors, and immature teratomas. The standard regimen is BEP (bleomycin, etoposide, cisplatin) over several cycles.
* Observation: For benign tumors or very early-stage malignant tumors with complete resection, close follow-up may be sufficient.
* Treatment plans are individualized based on tumor type, stage, and patient preferences.

## 4. What can I expect after treatment?

* Most patients respond very well to treatment, with high cure rates (over 80–90% for malignant OGCTs).
* Side effects of chemotherapy may include fatigue, nausea, hair loss, and risk of infection, but supportive care helps manage these.
* Surgery recovery depends on extent but is generally well tolerated.
* Regular follow-up with imaging and tumor markers is essential to monitor for recurrence.
* Fertility often recovers after treatment, especially with fertility-sparing surgery.

## 5. Will my diagnosis or treatment affect my ability to have a baby?

* Many ovarian germ cell tumors occur in young women, and fertility preservation is a key consideration.
* Fertility-sparing surgery (removing only the affected ovary) is standard whenever possible.
* Chemotherapy regimens used are designed to minimize long-term fertility impact.
* Most women resume normal menstrual cycles and retain the ability to conceive after treatment.
* Your care team can discuss fertility preservation options before treatment begins

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**CHORIOCARCINOMA**

**DEFINITION AND DESCRIPTION**

Choriocarcinoma is a rare and aggressive form of cancer that happens in your uterus or ovaries. The most common type, gestational choriocarcinoma is a type of gestational trophoblastic disease (GTD). GTD is a group of rare conditions that happens in pregnancy when tumors form from the placenta. The placenta provides oxygen and nutrients to a fetus through the umbilical cord.

Choriocarcinoma is most common in people who have a molar pregnancy (when the sperm and egg join incorrectly and make a hydatidiform mole). It can also happen after an ectopic pregnancy, a pregnancy that ends in miscarriage or even after a full-term pregnancy resulting in a birth.

Choriocarcinoma can spread quickly to other parts of your body, including your:

* Lungs.
* Uterine muscle layer.
* Lymph nodes.
* Liver or kidneys.
* Brain.
* Blood vessels.

Most cases of choriocarcinoma are cured by chemotherapy treatment.

**Types of choriocarcinoma**

There are two types of choriocarcinoma: gestational and non-gestational.

Gestational choriocarcinoma is more common. It refers to cancer developing during or shortly after pregnancy.

Non-gestational choriocarcinoma affects all sexes. It’s a type of germ cell tumor that can affect the ovaries or uterine lining, but isn’t related to a placenta. In males, it can develop in your testicles.

Gestational choriocarcinoma accounts for about 5% of all cases of GTD. GTD occurs in about 0.1% of all pregnancies in the United States. Gestational choriocarcinoma is still very rare — it occurs in fewer than 7 in 100,000 pregnancies in the U.S.

**Symptoms and Causes**

People with choriocarcinoma, especially people who were recently pregnant, may have the following symptoms:

* Irregular vaginal bleeding.
* Pelvic pain.

You could develop other symptoms if choriocarcinoma spreads to other parts of your body. For example, once it spreads to your lungs, you may cough or have trouble breathing. Other symptoms could include:

* Heavy bleeding, abnormal discharge or lumps in your vagina (if it spreads to your vagina).
* Seizures or headaches if it spreads to your brain.
* Pain in your abdomen if it spreads to your kidneys or liver.

**What causes choriocarcinoma?**

Choriocarcinomas happen when cells that form the placenta (called trophoblasts) become cancerous. Choriocarcinoma can develop early in pregnancy or happen after a pregnancy. About 50% of people with choriocarcinoma had a molar pregnancy. A molar pregnancy is when fluid-filled sacs or tumors develop inside your uterus instead of a placenta.

In non-gestational choriocarcinoma, cells in your ovaries, testicles or uterus start making human chorionic gonadotropin (hCG) and resemble trophoblasts under a microscope.

**How quickly does gestational choriocarcinoma develop?**

There isn’t a set time for how long it takes to develop. It can occur months or years after a pregnancy. It spreads quickly and is considered an aggressive type of cancer.

**Risk factors for this condition**

Anyone who’s been pregnant (miscarriage, ectopic, termination or full-term pregnancy) can get choriocarcinoma. But you’re most at risk if you’ve had a molar pregnancy.

Other risk factors include:

* Being younger than 20 or older than 40 during pregnancy.

**Complications of this condition**

Because this type of cancer spreads quickly, not getting treatment for choriocarcinoma can be fatal. With treatment, many people can achieve remission or be cured. As with most cancers, treating it at its earliest stages has the most successful results.

**Diagnosis and Tests**

A healthcare provider diagnoses choriocarcinoma with the following tests:

* Pelvic exam or physical exam to check for lumps or masses.
* Blood test to look for hCG (human gonadotrophin), which is high in people with choriocarcinoma.
* Blood tests to check liver and kidney function.
* Complete blood count (CBC).
* Pelvic ultrasound.
* Computed tomography (CT) scan.
* Magnetic resonance imaging (MRI).
* Chest X-ray.

These tests can also tell your provider if the cancer has spread.

**Management and Treatment**

Healthcare providers treat choriocarcinoma differently depending on its stage. Staging is how your provider rates your cancer based on the size of the tumor, and if it’s spread to areas outside of your uterus, among other factors. Your overall health and personal preferences are also considered when deciding on a treatment plan.

The main treatment for choriocarcinoma is chemotherapy. Chemotherapy is a drug that kills cancer cells. Some people may also need surgery to remove their uterus (hysterectomy), radiation or a combination of treatments.

After treatment, your healthcare provider will schedule follow-up exams to make sure the cancer doesn’t return.

**Is choriocarcinoma cancer curable?**

Yes, choriocarcinoma is curable. Treatment with chemotherapy is usually successful in curing it. The prognosis is better when choriocarcinoma is caught early, before it spreads to other parts of your body.

It’s also harder to cure if:

* You’ve had chemotherapy and it was unsuccessful.
* You develop the disease after a full-term pregnancy or birth of a child.
* HCG levels are higher than 40,000 mIU/ml (milli-international units per milliliter) before treatment. HCG is a hormone the placenta creates during pregnancy.
* You’ve had symptoms or were pregnant more than four months before treatment.

**Outlook / Prognosis**

The outlook for choriocarcinoma in its early stages is good. The survival rate for people with low-risk gestational choriocarcinoma is almost 100%. The survival rate for people with high-risk gestational choriocarcinoma is 94%.

Non-gestational choriocarcinoma (not related to a prior abnormal pregnancy/placental tissue) has a worse prognosis and is less chemosensitive, which means chemotherapy may not be as effective in killing the cancer cells.

**Can Stage 4 choriocarcinoma be cured?**

Stage 4 choriocarcinoma means the cancer has spread to other parts of your body like your brain and liver. Your healthcare providers will discuss your outlook with you, but it’s still possible to go into remission.

**Prevention**

No, you can’t prevent choriocarcinoma. If you’ve had a molar pregnancy, talk to your healthcare provider about your risk for choriocarcinoma.

**Living With**

Maybe. Many people are able to still have children after treatment for choriocarcinoma. It depends on your diagnosis. Discuss your desire for children with your healthcare provider so they know how to best treat you.

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

You should contact your healthcare provider if you develop unusual vaginal bleeding or pelvic pain, especially if you’ve had a molar pregnancy.

## **Common Chemotherapy Drugs**

| **Drug** | **Description** | **Common Side Effects** |
| --- | --- | --- |
| Methotrexate | Antimetabolite; inhibits DNA synthesis | Mucositis, nausea, liver toxicity, myelosuppression, stomatitis, fatigue |
| Dactinomycin (Actinomycin D) | Intercalates DNA, inhibits RNA synthesis | Nausea, vomiting, myelosuppression, alopecia, mucositis |
| Etoposide | Topoisomerase II inhibitor | Myelosuppression, alopecia, nausea, risk of secondary leukemia |
| Cyclophosphamide | Alkylating agent causing DNA crosslinking | Hemorrhagic cystitis, myelosuppression, nausea, alopecia |
| Vincristine (Oncovin) | Microtubule inhibitor | Peripheral neuropathy, constipation, hair loss, myelosuppression |
| Cisplatin | Platinum-based DNA crosslinker | Nephrotoxicity, ototoxicity, nausea, neuropathy, myelosuppression |
| Paclitaxel | Microtubule stabilizer (used in some regimens) | Peripheral neuropathy, myelosuppression, hypersensitivity reactions |

## 2. Common Chemotherapy Regimens

| **Regimen Name** | **Components** | **Use Case** | **Notes on Toxicity** |
| --- | --- | --- | --- |
| Methotrexate alone | Methotrexate ± folinic acid rescue | Low-risk GTN | Well tolerated; requires folinic acid to reduce toxicity |
| Dactinomycin alone | Dactinomycin (pulsed or 5-day) | Low-risk, methotrexate-resistant | More toxic than methotrexate; nausea, myelosuppression |
| EMA/CO | Etoposide, Methotrexate, Actinomycin D / Cyclophosphamide, Vincristine | Standard for high-risk GTN | Effective but with significant myelosuppression and neuropathy |
| EMA/EP | Etoposide, Methotrexate, Actinomycin D / Etoposide, Cisplatin | Alternative high-risk regimen | Cisplatin adds nephrotoxicity and neuropathy risk |
| MEA | Methotrexate, Etoposide, Actinomycin D | High-risk GTN | Comparable success with reduced toxicity vs EMA/CO |
| MAC | Methotrexate, Actinomycin D, Chlorambucil | Historical regimen | More toxic, less used now |
| CHAMOCA | Methotrexate, Dactinomycin, Cyclophosphamide, Doxorubicin, Melphalan, Hydroxyurea, Vincristine | Older regimen, now obsolete | High toxicity, not recommended |

## 3. Side Effects Overview

* Myelosuppression: Common with most agents, leading to anemia, neutropenia (infection risk), and thrombocytopenia (bleeding risk).
* Nausea and Vomiting: Managed with antiemetics; common with cisplatin, cyclophosphamide, and etoposide.
* Alopecia: Hair loss is common with etoposide, cyclophosphamide, and vincristine.
* Neurotoxicity: Vincristine and cisplatin can cause peripheral neuropathy (numbness, tingling).
* Nephrotoxicity and Ototoxicity: Mainly from cisplatin; requires hydration and monitoring.
* Mucositis and Stomatitis: Particularly with methotrexate and dactinomycin.
* Hemorrhagic cystitis: Risk with cyclophosphamide; prevented with hydration and mesna.
* Secondary malignancies: Rare but possible with etoposide and alkylating agents.

## 4. Treatment Monitoring

* hCG levels: Monitored frequently to assess treatment response.
* Blood counts: Regular CBC to detect myelosuppression.
* Renal and liver function: Monitored due to potential toxicity.
* Supportive care: Includes antiemetics, growth factors (e.g., G-CSF), hydration, and infection prophylaxis.

## **Gestational Choriocarcinoma (GC)**

* Mutation Burden:
  + GC tumors exhibit a high number of somatic mutations, with one study showing >7 times more mutations than NGC tumors.
  + Whole-exome sequencing of 20 GCs revealed thousands of non silent mutations, including several driver mutations.
* Key Mutated Genes:
  + Mutations predominantly affect chromatin remodeling genes such as ARID1A, SMARCD1, and EP300.
  + Common oncogenes like TP53 and KRAS are typically not mutated in GC.
  + Copy-neutral loss of heterozygosity (CN-LOH) with androgenetic origins (monospermic or dispermic) is characteristic.
  + Recurrent copy number alterations (CNAs), especially gains on chromosome 1q21.1–q44, are associated with poorer prognosis.
* Genomic Features:
  + GC shows unique patterns of CN-LOH differentiating it from non-gestational tumors.
  + Pathway enrichment analyses highlight extracellular matrix-receptor interactions.
* Clinical Implications:
  + The genomic profile explains the high chemosensitivity and unique biology of GC.
  + Some cases show mutations in genes involved in epigenetic regulation, suggesting potential therapeutic targets.

## 2. Non-Gestational Choriocarcinoma (NGC)

* Mutation Burden:
  + NGC tumors have fewer somatic mutations compared to GC.
  + A pilot study identified mutations in the DNAJB9 gene, a regulator of p53, which was mutated only in NGC samples.
* Key Findings:
  + Dysfunction of DNAJB9 leads to p53 overexpression, implicating this pathway in NGC tumor biology.
  + NGC shows distinct mutation spectra and pathway enrichments (e.g., graft-versus-host disease pathways).

**Epidemiology of Choriocarcinoma**

Incidence:

Choriocarcinoma is a rare malignancy arising from trophoblastic tissue, with incidence varying by region and population.

A large national study reported an incidence of 1 case per 66,775 live births (non-molar gestational choriocarcinoma) .

Incidence increases with maternal age:

Under 20 years: ~1 in 223,494 viable pregnancies

Ages 30–34: ~1 in 80,227

Ages 40–45: ~1 in 41,718 .

Other studies report incidence rates ranging from 2 to 7 cases per 100,000 pregnancies in the U.S. and Europe, with higher rates in Asia (up to 5–200 per 100,000 pregnancies) and some Latin American countries .

In the Philippines (1970–74), the incidence was reported as high as 17.4 per 100,000 live births .

Internationally, incidence varies widely:

India: up to 1 in 500–600 pregnancies

Mexico, Paraguay, Sweden: about 1 in 50,000 pregnancies .

Age Distribution:

Incidence is higher at the extremes of reproductive age, especially in women aged 40 years and older, who have a 5–15 times higher risk compared to younger women .

Slightly increased risk is also noted in women under 20 years.

Geographic and Ethnic Variation:

Higher incidence reported in Asia (China, India, Indonesia, Thailand) and parts of Africa (Nigeria), with rates up to 99 per 100,000 in some regions .

Lower incidence in Europe, North America, Australia, and some Latin American and Middle Eastern countries .

Ethnic differences include higher rates among Eurasians in South Asia compared to Chinese, Malaysian, or Indian populations.

African Americans in the U.S. have a lower incidence compared to Caucasians but worse survival rates .

Latin American populations, Mexicans, and Filipinos have elevated rates compared to Japanese and Chinese .

Prevalence and Mortality:

Prevalence in the U.S. is approximately 0.075 to 0.01 per 100,000 individuals .

The 5-year overall mortality rate is low (~2%) after excluding placental site and epithelioid trophoblastic tumors.

High-risk patients have a higher mortality rate (~12%), and those with FIGO score ≥13 have a 5-year mortality of ~38% .

* Trends:
  + Some studies report a decline in incidence globally, likely due to improved chemotherapy and decreased molar pregnancy rates

**Differential Diagnosis (DDx) of Choriocarcinoma**

## 1. Gestational vs. Non gestational Choriocarcinoma

* Gestational choriocarcinoma:
  + Originates from placental trophoblast after a pregnancy event (normal, molar, ectopic).
  + More sensitive to chemotherapy and has a better prognosis.
  + May metastasize hematogenously to lungs, brain, liver, etc.
  + Diagnosis supported by history of recent pregnancy and presence of paternal DNA (via genomic testing).
* Non gestational choriocarcinoma:
  + Arises from germ cells in the ovary (very rare, <1% of ovarian germ cell tumors).
  + Less chemosensitive and associated with poorer prognosis.
  + Can mimic ectopic pregnancy or other adnexal masses.
  + Occurs in prepubertal girls or women without pregnancy history.
  + Diagnosis challenging; requires DNA polymorphism analysis or clinical correlation.

## 2. Other Conditions to Differentiate From

| **Condition** | **Key Features** | **Differentiation Points** |
| --- | --- | --- |
| Ectopic pregnancy | Positive β-hCG, adnexal mass, abdominal pain | Usually early pregnancy history, ultrasound findings, no tumor mass |
| Hydatidiform mole (complete or partial) | Abnormal pregnancy with molar tissue, elevated β-hCG | Ultrasound shows "snowstorm" pattern; histology differs |
| Invasive mole | Persistent trophoblastic tissue invading myometrium | History of molar pregnancy, elevated β-hCG, uterine mass on imaging |
| Placental site trophoblastic tumor (PSTT) | Rare trophoblastic tumor, lower β-hCG levels, slow growing | Different histology, immunohistochemistry, less β-hCG elevation |
| Epithelioid trophoblastic tumor (ETT) | Rare, slow growing, β-hCG mildly elevated | Histology and immunoprofile distinct from choriocarcinoma |
| Other germ cell tumors with trophoblastic differentiation | Mixed germ cell tumors containing choriocarcinoma elements | Requires histopathology and immunohistochemistry |
| Primary ovarian tumors (e.g., dysgerminoma, immature teratoma) | May present with adnexal mass, elevated tumor markers | Differentiated by histology and tumor marker profile |
| Metastatic choriocarcinoma to ovary | From uterine or other gestational sites | Clinical history and imaging to identify primary site |
| Other malignancies with elevated β-hCG | Rarely, other tumors (e.g., lung, bladder) produce β-hCG | Correlation with clinical and imaging findings |

## **Doctor-Patient Conversation: Choriocarcinoma**

Doctor: Hello, I want to discuss your diagnosis of choriocarcinoma and explain what this means and how we will manage it. How are you feeling today?

Patient: I’m quite worried, doctor. What exactly is choriocarcinoma?

Doctor: Choriocarcinoma is a rare but serious tumor that arises from the cells that normally develop into the placenta during pregnancy. It can occur after a normal pregnancy, miscarriage, or molar pregnancy. The good news is that with modern treatment, most women are cured.

Patient: What tests will I need now?

Doctor: We will do blood tests to measure your hCG levels, which help us monitor the tumor activity. You’ll also have imaging tests like ultrasound, CT scans, and possibly MRI to see where the tumor is and if it has spread. We may also do chest X-rays to check your lungs, as this tumor can spread there.

Patient: What treatments will I need?

Doctor: Treatment depends on how advanced the tumor is. Most patients receive chemotherapy, which is very effective in choriocarcinoma. If the tumor is localized and low risk, chemotherapy alone may be enough. For higher risk or metastatic disease, we may combine chemotherapy with surgery or radiation if needed. We will tailor the treatment to your specific situation.

Patient: What can I expect during and after treatment?

Doctor: Chemotherapy is usually given in cycles, and we monitor your hCG levels closely to see how well the tumor is responding. Side effects can include fatigue, nausea, and hair loss, but we have ways to manage these. After treatment, you’ll have regular follow-up appointments with blood tests and imaging to ensure the tumor is gone and to catch any recurrence early.

Patient: Will this affect my ability to have children in the future?

Doctor: Many women retain their fertility after treatment, especially since we aim to preserve the uterus and ovaries whenever possible. We will discuss fertility preservation options with you before starting treatment and support you throughout.

Patient: How often will I need monitoring after treatment?

Doctor: Initially, we monitor your hCG levels every two weeks until they return to normal, then less frequently over the following months. Because choriocarcinoma can recur, especially with future pregnancies, we ask for hCG testing after any subsequent pregnancy as well.

Patient: What support is available during this process?

Doctor: You will have access to a specialist team including oncologists, nurses, and counselors. We provide 24/7 advice lines, and you’ll have a clinical nurse specialist to guide you through treatment and follow-up. We also offer written information and support groups.

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**YOLK SAC TUMOR**

**DEFINITION AND DESCRIPTION**

A yolk sac tumor — also called an endodermal sinus tumor — is a cancer that forms in cells that eventually become eggs or sperm. A type of germ cell tumor, yolk sac tumors usually start in either your ovaries or testicles. But in rare cases, these masses form in places other than your reproductive organs.

Although they’re rare overall, yolk sac tumors are the most common type of cancerous germ cell tumor diagnosed in children. They grow fast and spread quickly. They’re potentially fatal without treatment. But with early diagnosis, treatments can slow or prevent cancer spread. Early-stage yolk sac tumors are often curable.

**Types of yolk sac tumors**

Types of yolk sac tumors include:

* **Testicular yolk sac tumors**. A form of testicular cancer, these tumors are most common in children under 3 and people in their 20s and 30s. They’re usually diagnosed before they spread, while they’re curable.
* **Ovarian yolk sac tumors**. This aggressive form of ovarian cancer is most common in people 20 years old or younger. One-third of diagnoses involve children too young to have gotten their periods.

Like other types of germ cell tumors, yolk sac tumors sometimes form in places outside of your reproductive organs, in places like your brain, chest, abdomen or tailbone. These are called extragonadal germ cell tumors.

**Symptoms and Causes**

Signs and symptoms of a yolk sac tumor depend on where it’s located and may include:

* A firm, painless lump in a testicle
* Swelling in your abdomen or a mass (ovaries)
* Abdominal pain or back pain (ovaries)
* Changes in your bowel habits (ovaries)
* Irregular periods, including heavy period bleeding (ovaries)
* Headaches or vision issues (brain)
* Cough and shortness of breath (chest)
* A swollen area resembling a bruise or infected bump (in your tailbone)

**What causes yolk sac tumors?**

Medical researchers don’t know what causes yolk sac tumors. Like all cancers, yolk sac tumors form when changes to the genes in cell DNA (mutations) cause cells to multiply too fast. Eventually, they form masses. Without treatment, the cancer can spread.

But experts are still researching what starts this process in the first place.

**Diagnosis and Tests**

Diagnosis involves a physical examination to check for signs of a yolk sac tumor, like unusual lumps or swelling in your abdomen or testicles. Your healthcare provider will also ask about your symptoms.

Tests you may need include:

* **Blood tests**. Your provider will check your blood for high levels of alpha-fetoprotein (AFP). Nearly all yolk sac tumors secrete this protein.
* **Imaging tests**. Computed tomography (CT) scans and magnetic resonance imaging (MRI) are the most common imaging tests providers use to detect these tumors.
* **Surgical excision**.Your provider will remove the entire mass (and sometimes, the entire organ containing the mass) and test it in a lab for cancer cells. This is the only way to be sure a mass is a yolk sac tumor.

**Staging yolk sac tumors**

Healthcare providers stage yolk sac tumors to determine how advanced the cancer is and find the best treatment options. Using information like tumor size and the extent of cancer spread, they assign a number or “stage.” Lower numbers mean that cancer is in the early stages. Higher numbers mean more advanced cancer.

Testicular yolk sac tumors range from stages 1 to 3:

* **Stage 1**: The cancer is only in your testicle.
* **Stage 2**: Cancer has spread to your lymph nodes.
* **Stage 3**: Cancer cells have spread to other organs.

Ovarian yolk sac tumors range from stages 1 to 4:

* **Stage 1**: The cancer hasn’t spread beyond one or both ovaries.
* **Stage 2**: Cancer cells have spread below your pelvis, but they’re not in your lymph nodes.
* **Stage 3**: The cancer has spread to your lymph nodes and the layer of tissue lining your abdomen (peritoneum) that’s outside your pelvis.
* **Stage 4**: Cancer has spread to tissues and organs other than your peritoneum.

**Management and Treatment**

Treatment involves surgery to remove all traces of the yolk sac tumor. This typically means removing the entire affected testicle (orchiectomy) or ovary (oophorectomy). Your healthcare provider may also remove lymph nodes if the cancer has spread there.

Chemotherapy treatment (chemo) usually follows. This treatment uses chemotherapy drugs to kill any cancer cells that may remain. If a yolk sac tumor is so large that surgery may pose risks, you may need chemotherapy before surgery to shrink the tumor.

**BEP chemotherapy for yolk sac tumors**

BEP is a combination drug therapy for yolk sac tumors. Depending on the cancer stage and your response to treatment, you may need one or more rounds of BEP. BEP includes the chemotherapy drugs:

* Bleomycin sulfate
* Etoposide phosphate
* Cisplatin (Platinol®)

When taken together, these drugs are powerful yolk sac tumor fighters.

**Outlook / Prognosis**

Yolk sac tumors are life-threatening without treatment. This is why early diagnosis and treatment are so important. As with most cancers, the earlier you get treatment, the better your prognosis (outcome).

Still, your prognosis depends on different factors you’ll need to discuss with your provider, like the cancer stage and your body’s response to treatment. Alpha-fetoprotein (AFP) levels are also important. Lower AFP levels before chemotherapy typically suggest a better outcome.

**Survival rates**

The good news is that treatments like surgery and BEP improve the survival rate of people diagnosed with yolk sac tumors. For example, nearly all stage 1 testicular yolk sac tumors are curable with this treatment. A recent study tracking the survival of people treated for ovarian yolk cell tumors showed that 91.5% with early-stage cancer were alive five years later. That number was 74.8% for people who had cancer spread beyond their ovaries.

**Living With**

Navigating a yolk sac tumor diagnosis can be hard. In addition to the stress of having cancer, you also have to manage the challenges of managing treatment side effects. For example, yolk sac treatment often requires several rounds of chemo, which can cause unpleasant side effects.

Before treatment, ask your healthcare provider what side effects to expect and how to manage them. Ask them to connect you with available resources that can help with pain management, like palliative care. This care option can help you navigate treatment side effects, no matter your cancer stage or prognosis.

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

Surveillance (regular check-ups with your provider after cancer treatment) is essential. This is especially the case within the first five years following treatment. Surveillance involves:

* Physical scans
* CT scans of your abdomen and pelvis
* Blood tests (to check your AFP levels)

The purpose of surveillance is to make sure the cancer isn’t back. If your healthcare provider detects it, they can treat it right away.

## **Epidemiology**

YSTs can be seen in males and females, involving the testis, ovary, and other sites such as the mediastinum.

In males: YSTs of the testis are located in the testis parenchyma; they have bimodal age distribution involving children and adults.

* Pure YST is the most common testicular neoplasm seen in infants and prepubertal children up to 3 years of age, accounting for 30% of testicular germ cell tumors in this age group, with a median age of 1.5 years.
* YST is seen in postpubertal age groups and adults with an age averaging 25-30 years. In this age range, YST is rarely "pure" and usually occurs in combination with embryonal carcinoma (EC) or other germ cell components (mixed [nonseminomatous] germ cell tumors) . YST components are present in 40-50% of nonseminomatous germ cell tumors in the adult testis.

In females: YST is the second most common malignant ovarian germ cell tumor after dysgerminoma, typically affecting children, adolescents, and young adults in the premenopausal period (median age: 19 years) and extremely rarely during the postmenopausal stage.It often coexists with other germ cell tumors such as embryonal carcinoma or dysgerminoma. Primary YSTs are commonly seen in ovaries and gonadal ridge. However, around 20% of YSTs occur at extragonadal midline sites, including the female genital tract (vagina, cervix), sacrococcygeal region, retroperitoneum, mediastinum, head, neck, and central nervous system.Primary YSTs will rarely arise from the endometrium.

In children, YSTs are more common in Asians than in White or Black people. In adults, these tumors are more common in White individuals than in other races.

There are several other tumors that could present in a similar fashion and need to be distinguished. Following are some important differentials with their distinguishing features:

* **Clear Cell Carcinoma**: stains positive for cytokeratin, cytokeratin 7, and epithelial membrane antigen, while stains negative for glypican-3 and alpha-fetoprotein. Yolk sac tumors stain negative for both cytokeratin 7 and epithelial membrane antigen.
* **Sertoli-Leydig Cell Tumor**: positive for inhibin, calretinin, and steroidogenic factor 1 (SF1), negative for AFP and glypican 3.
* **Juvenile Granulosa Cell Tumor**: it has morphological similarities with the yolk sac tumor, but the juvenile granulosa cell tumor is positive for inhibin and negative for SALL4, AFP, and glypican 3.
* **Metastatic Hepatocellular Carcinoma**: considered in conjunction with clinical history, negative for (Sal-like protein 4) SALL4, while strongly positive in yolk sac tumors.
* **Dysgerminoma/Seminoma**: stains positive for placental alkaline phosphatase (PLAP), CD117, and octamer-binding transcription factor 4 (Oct-4)
* **Embryonal Carcinoma**: stains positive for placental alkaline phosphatase (PLAP), cytokeratin, CD30, and octamer-binding transcription factor 4 (Oct-4).
* **Granulocytic Sarcoma**: stains positive for CD117, leukocyte common antigen (LCA), and myeloperoxidase (MPO).
* **Melanoma**: stains positive for S-100.
* **Lymphoma**: stains positive for leukocyte common antigen (LCA).
* While yolk sac tumors stain negative for CD117, CD30, S-100, leukocyte common antigen (LCA), myeloperoxidase (MPO), and octamer-binding transcription factor 4 (Oct-4).

**Staging of Yolk Sac Tumors (YSTs)**

## 1. Testicular Yolk Sac Tumor Staging

* Stage I: Tumor confined to the testicle.
* Stage II: Cancer has spread to regional lymph nodes (typically retroperitoneal).
* Stage III: Distant metastases to other organs (lungs, liver, brain, etc.).

## 2. Ovarian Yolk Sac Tumor Staging

Ovarian malignant germ cell tumors, including yolk sac tumors, use the FIGO staging system, similar to epithelial ovarian cancers:

* Stage I: Tumor limited to one or both ovaries.
  + IA: Tumor limited to one ovary, capsule intact, no tumor on surface, negative washings.
  + IB: Tumor involves both ovaries, capsules intact, no tumor on surface, negative washings.
  + IC: Tumor limited to one or both ovaries with any of the following: capsule rupture, tumor on ovarian surface, positive peritoneal washings.
* Stage II: Tumor involves one or both ovaries with pelvic extension (below pelvic brim) or implants.
  + IIA: Extension and/or implants on uterus and/or fallopian tubes.
  + IIB: Extension to other pelvic tissues.
* Stage III: Tumor involves one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal lymph nodes.
  + IIIA: Microscopic peritoneal metastasis beyond pelvis.
  + IIIB: Macroscopic peritoneal metastasis ≤2 cm.
  + IIIC: Peritoneal metastasis >2 cm and/or regional lymph node metastasis.
* Stage IV: Distant metastasis beyond the peritoneal cavity (e.g., liver parenchyma, lungs).

## **Genomic Findings:**

* Mutation Profile:
  + YSTs exhibit very infrequent TP53 mutations in typical cases, but tumors arising in patients with abnormal gonadal development may harbor both KRAS and TP53 mutations.
  + Significant somatic driver mutations include KRAS and KIT, which are recurrently mutated in YSTs.
  + Copy number alterations (CNAs) are common, with frequent deletions of ARID1A and PARK2 and amplifications of ZNF217, CDKN1B, and KRAS.
* Chemoresistance Associations:
  + Microsatellite instability status and specific mutational signatures correlate with resistance to cisplatin-based chemotherapy.
  + Overexpression of the gene OVOL2 has been implicated in cisplatin resistance in YSTs, suggesting a role in treatment response.
* Epigenetic and Expression Patterns:
  + YSTs show overexpression of endodermal genes such as GATA6 and FOXA2, whose binding sites are hypomethylated, indicating epigenetic regulation.
  + Tumor suppressor genes like RASSF1, APC, RUNX3, and HIC1 are often hypermethylated, contributing to tumorigenesis.
  + Activation of the TGF-β pathway is noted, linked to the overexpression of key transcription factors.
* Chromosomal Alterations:
  + Gains of chromosomes 1q, 12p, and 20q and losses of 1p, 4q, 6q, and 16 are recurrent in YSTs.
  + The presence of isochromosome 12p, common in adult germ cell tumors, is also observed in some YST cases.

**Yolk Sac Tumors (YSTs): Treatment Drugs and Their Side Effects**

## 1. Standard Treatment Approach

* Surgery:
  + Primary treatment involves surgical removal of the tumor (e.g., unilateral salpingo-oophorectomy for ovarian YST).
  + Surgery aims to remove visible tumours and obtain accurate staging.
* Chemotherapy:
  + Essential for malignant YSTs due to their aggressive nature and tendency to metastasize.
  + The most effective and commonly used chemotherapy regimen is BEP:
    - Bleomycin
    - Etoposide
    - Platinum-based drug (usually cisplatin; carboplatin sometimes used)

## 2. Common Chemotherapy Drugs Used

| **Drug** | **Role** | **Common Side Effects** |
| --- | --- | --- |
| Bleomycin | Causes DNA strand breaks | Pulmonary toxicity (fibrosis), skin changes, fever |
| Etoposide | Topoisomerase II inhibitor | Myelosuppression, nausea, alopecia, risk of secondary leukemia |
| Cisplatin | Platinum DNA crosslinker | Nephrotoxicity, ototoxicity (hearing loss), nausea, neuropathy |
| Carboplatin | Alternative platinum agent | Less nephrotoxicity than cisplatin but causes myelosuppression |
| Cyclophosphamide (occasionally) | Alkylating agent | Hemorrhagic cystitis, myelosuppression, nausea |
| Vincristine (occasionally) | Microtubule inhibitor | Peripheral neuropathy, constipation |

## 3. Side Effects and Management

* Common Side Effects:
  + Nausea and vomiting: Managed with antiemetics.
  + Myelosuppression: Leads to low white blood cells (infection risk), anemia, and bleeding risk; requires blood count monitoring and sometimes growth factors.
  + Fatigue and hair loss: Common but usually reversible.
  + Pulmonary toxicity: From bleomycin; lung function monitoring recommended.
  + Nephrotoxicity and ototoxicity: From cisplatin; requires hydration and audiology monitoring.
  + Infections and fever: Due to immunosuppression; prompt treatment essential.
* Psychosocial Impact:
  + Chemotherapy can cause anxiety, stress, and impact quality of life, especially in children. Supportive care and counseling are important.

## 4. Treatment Outcomes

* Nearly all stage I testicular YSTs are curable with surgery and chemotherapy.
* For ovarian YSTs, 5-year survival is approximately 91.5% for early-stage and 74.8% for advanced disease.
* Chemotherapy alone can sometimes cure vaginal YSTs in infants and children, avoiding extensive surgery.
* Long-term follow-up is essential to monitor for recurrence and late effects of treatment.

## 5. Surveillance Post-Treatment

* Regular monitoring of serum alpha-fetoprotein (AFP) levels is critical to detect recurrence early.
* Imaging studies (ultrasound, CT, MRI) are used as indicated.
* Follow-up intervals typically start monthly and become less frequent over years.

## **Doctor-Patient Conversation: Yolk Sac Tumor**

Doctor: Hello, I want to discuss your diagnosis of a yolk sac tumor and explain what it means and how we will treat it. How are you feeling today?

Patient: I’m quite worried, doctor. What exactly is a yolk sac tumor?

Doctor: A yolk sac tumor is a rare and aggressive type of cancer that arises from the cells that normally develop into eggs or sperm. It most commonly occurs in children and young adults, often in the ovaries or testes. Because it grows quickly, early diagnosis and treatment are very important.

Patient: What tests will I need before treatment?

Doctor: We will do blood tests to measure a protein called alpha-fetoprotein, or AFP, which is usually very high in yolk sac tumors. Imaging tests like ultrasound, CT, or MRI will help us see the size and location of the tumor and whether it has spread. Surgery will also be needed to remove the tumor and get tissue for a definitive diagnosis.

Patient: What treatments will I need?

Doctor: Treatment usually involves surgery to remove the affected ovary or testicle. Because these tumors can spread quickly, chemotherapy is almost always recommended after surgery to kill any remaining cancer cells. The most common chemotherapy regimen is called BEP, which includes three drugs: bleomycin, etoposide, and cisplatin.

Patient: What side effects should I expect from the chemotherapy?

Doctor: Chemotherapy can cause side effects like nausea, fatigue, hair loss, and a lowered immune system, which can increase infection risk. Bleomycin can affect your lungs, so we will monitor your lung function closely. Cisplatin can affect your kidneys and hearing, so we’ll take steps to protect those. Most side effects are manageable, and many improve after treatment ends.

Patient: What can I expect after treatment? Will I be able to have children?

Doctor: Many patients do very well with treatment. The prognosis is good, especially if the tumor is caught early. Because we try to preserve as much healthy tissue as possible, many women and men retain their fertility after treatment. We usually recommend waiting about two years after treatment before trying to conceive, to ensure the cancer is fully treated.

Patient: How will you monitor me after treatment?

Doctor: We will regularly check your AFP levels with blood tests to make sure the tumor has not returned. Imaging studies will also be done as needed. Follow-up visits are usually frequent at first and then spaced out over time.

Patient: Is there support available during this process?

Doctor: Absolutely. We have a multidisciplinary team including oncologists, nurses, and counselors to support you. There are also patient groups and resources to help you through treatment and recovery.

**What questions should I ask my healthcare provider?**

Questions to ask include:

* What is the cancer stage?
* Which treatments will I need?
* What side effects should I expect during treatment?
* How will we know if the treatment worked?

[Yolk Sac Tumor: Symptoms, Diagnosis & Prognosis](https://my.clevelandclinic.org/health/diseases/yolk-sac-tumor#overview)

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### **CNS LYMPHOMA**

**DEFINITION AND DESCRIPTION**

CNS lymphoma is a rare, aggressive cancer that develops in your central nervous system (CNS). Tumors may form in your brain, spinal cord, spinal fluid and (as it’s so close to your brain) your eye. It’s a type of non-Hodgkin lymphoma.

CNS lymphoma starts in white blood cells called lymphocytes, which are part of your lymphatic system. Your lymphatic system is an important part of your immune system. It helps your body fight infections and diseases. When the lymphoma starts in your CNS and isn’t found anywhere else in your body, it’s called primary CNS lymphoma. If lymphoma is in other parts of your body, as well as in your CNS, it’s called secondary CNS lymphoma.

Although anyone can get this cancer, you’re more likely to be diagnosed if you’re a male who has a weakened immune system from a condition like HIV and AIDS. People over 65 are also more at risk. Still, this cancer is extremely rare. Only about 1,500 new cases are diagnosed in the U.S. each year.

No matter your unique situation, your healthcare team will work with you to find the right treatment to fight CNS lymphoma.

## **Symptoms and Causes**

Symptoms depend on where the tumor is located. For instance, CNS lymphoma may not cause symptoms if it’s in the membrane covering your brain and spinal cord (meninges). But a tumor near your eyes often causes vision changes. If the mass occurs near the area of your brain that controls movement, you could have weakness or coordination changes.

Symptoms of CNS lymphoma may include:

* Nausea and vomiting
* Weakness in your arms, legs or face
* Weakness affecting one side of your body (hemiparesis)
* Hearing loss
* Difficulty swallowing (dysphagia)
* Signs of brain pressure (headaches, confusion)
* Vision problems (blurry vision, seeing double, floaters)
* Changes in your mental state (trouble speaking, memory loss, feeling sluggish)
* Seizures (that may become more frequent over several days or weeks)
* Trouble controlling when you pee or poop (urinary and fecal incontinence)

### **What causes CNS lymphoma?**

Like other types of lymphoma, CNS lymphoma forms when cells in lymph tissue start to behave abnormally. They multiply out of control and overtake healthy cells. With CNS lymphoma, the cells that start growing abnormally are usually white blood cells (lymphocytes) called B cells.

Researchers aren’t sure what causes a lymphocyte to transform into a cancer cell. But they’ve identified factors that may increase your risk of CNS lymphoma.

### **Risk factors for CNS lymphoma**

Certain conditions associated with having a weakened immune system may increase your risk of CNS lymphoma. Risk factors include:

* HIV/AIDS (especially if you have an active Epstein-Barr infection)
* Wiskott-Aldrich syndrome (WIS)
* Common variable immunodeficiency state (CVID)
* Ataxia-telangiectasia
* Taking immunosuppressant drugs following an organ transplant

## **Diagnosis and Tests**

Your healthcare provider may recommend different procedures and tests to diagnose CNS lymphoma. Cancer staging also takes place during diagnosis. Cancer staging helps providers determine how advanced the cancer is and which treatments will likely work best.

You may need:

* Exams. Your provider will check the health of your brain, spinal cord and eyes. They’ll perform a neurological exam to check your CNS. They may do a slit lamp exam to find signs of a tumor behind your eye.
* Imaging tests. Your provider may order an MRI, CT scan or PET scan to see where cancer is located inside of your body. CNS lymphoma rarely spreads beyond your central nervous system, but it may spread quickly within it.
* Blood tests. Blood tests allow your provider to check your cells for signs of cancer. Tests include a complete blood count, blood chemistry study and an HIV test.
* Tissue and fluid tests. Your provider may remove a sample of fluid or tissue from your spinal fluid, bone marrow or the tumor itself to test for cancer cells.

## **Management and Treatment**

Not everyone agrees on the best treatment for CNS lymphoma. Instead, your healthcare team will suggest a care plan based on various factors, like your age, your HIV/AIDS status and whether the cancer is newly diagnosed or recurrent (returned after treatment). Treatment will likely involve a combination of therapies.

Treatments for CNS lymphoma include:

* Chemotherapy. Chemotherapy uses drugs to kill cancer cells. High doses of a chemotherapy drug called methotrexate (HD-MTX) are often used to treat newly diagnosed CNS lymphoma.
* Radiation. Radiation uses beams of energy to kill cancer cells. One type of radiation treatment for symptom relief is whole-brain radiation. It destroys cancer cells throughout your brain.
* Targeted therapy. Targeted therapy uses substances like proteins and antibodies to attack cancer cells. Rituximab and ibrutinib are targeted therapy treatments that your provider may recommend.
* Stem cell transplant. During a stem cell transplant, you receive healthy blood cells to replace blood cells damaged during cancer treatments like chemotherapy and radiation.
* Clinical trial. Your provider may recommend you take part in a clinical trial to test new treatments. Current trials are studying the effectiveness of new targeted therapy drugs and new combinations of chemotherapy drugs in CNS lymphoma treatment.

If you’re HIV-positive or have AIDS, you’ll continue antiretroviral therapy (ART) while you receive treatments for CNS lymphoma.

#### **Complications/side effects of treatment**

Treatments for CNS lymphoma can cause side effects that your healthcare provider will discuss with you beforehand. For example, whole-brain radiation destroys cancer cells in your brain. But it may also lead to several severe side effects that can impact your brain function. All treatment options pose potential risks.

Discuss the benefits and risks of your treatment plan with your provider. Ask if they recommend palliative care. This treatment can help you manage side effects and the overall impact cancer has on your life.

## **Outlook / Prognosis**

CNS lymphoma is a fast-spreading cancer that often returns following treatment. Still, your prognosis (chance of recovery) depends on several unique factors, including:

* Your age
* Your overall health
* Your HIV status
* The location of the tumor
* The result of your blood chemistry studies (which can tell how the cancer may be impacting your organs)

Your healthcare team will work with you to find the treatment plan that gives you the best chance of survival without sacrificing your quality of life.

#### **Survival rate for CNS lymphoma**

Researchers report on cancer survival rates by tracking how many people with a certain cancer diagnosis are alive after a set time, usually five years. The five-year survival rate for people with CNS lymphoma is 30%. This means that 3 out of 10 people diagnosed with CNS lymphoma are alive five years later.

Still, these numbers are general. They don’t factor in other specifics that affect prognosis. For instance, outcomes are usually better if you’re not immunocompromised or if the lymphoma hasn’t spread beyond your brain. Survival rates also don’t consider the impact that new treatments may have on your life expectancy.

Your provider is your best resource for explaining how your health and unique cancer diagnosis will shape your likely outcome.

## **Living With**

Living with lymphoma is hard. You may feel anxious about what tests or treatments lie ahead. You may not know how to share what you’re feeling with others.

Now, more than ever is the time to reach out and take advantage of every available resource. This may mean reaching out to loved ones, even if it’s difficult. It may mean asking your healthcare provider about palliative care or support groups. Everyone’s cancer journey is different. But it’s essential to connect with others every step of the way.

## **Differential Diagnosis of CNS Lymphoma**

1. High-grade gliomas (glioblastoma multiforme)
2. Metastatic brain tumors
3. Tumefactive demyelinating lesions (TDLs)
4. Neurotoxoplasmosis (especially in immunocompromised patients)
5. Cerebral abscess
6. Secondary CNS lymphoma (systemic lymphoma with CNS involvement)
7. Posttransplant lymphoproliferative disorder (PTLD)
8. Intravascular large B-cell lymphoma
9. Germinoma (midline CNS tumors)
10. Lymphomatoid granulomatosis
11. Progressive multifocal leukoencephalopathy (PML)
12. Other infections (e.g., fungal, bacterial encephalitis)
13. Primary CNS vasculitis
14. Other CNS tumors (e.g., meningioma, medulloblastoma in children)

**EPIDEMIOLOGY**

CNS lymphoma is decreasing in persons living with AIDS due to the advent of HAART, but its incidence is rising in older adults.The disease is rare in pediatric populations. PCNSL has an annual incidence of approximately 1700 cases in the United States or approximately 0.5 per 100,000 per year. PNCSL comprises 3% of all primary brain tumors and 2% to 3% of all cases of NHL. Immunocompetent patients are often diagnosed between ages 50 and 70, whereas immunocompromised patients present earlier, typically in their 30s and 40s. Men are affected more than women in both immunocompetent and immunocompromised groups, though there is no sex-based predilection in patients who develop CNS lymphoma after solid organ transplantation. Other patient populations at risk for PCNSL include those with ataxia-telangiectasia, Wiskott-Aldrich syndrome, and other immunodeficiency syndromes.

The vast majority—more than 90%—of PCNSL cases are diffuse large B-cell lymphoma; primary forms of T-cell and Burkitt lymphomas and lower-grade lymphoproliferative conditions have also been reported.Within the CNS, PCNSL most commonly arises in the frontal lobe and the basal ganglia, with the brainstem, cerebellum, and spinal cord less commonly affected. Most immunocompetent patients have a solitary brain mass, with multiple lesions observed in 20% to 40% of cases.

Up to 25% of patients with PCNSL develop intraocular lymphoma, and primary intraocular lymphoma ultimately disseminates to the CNS more than 80% of the time. Concurrent cerebrospinal fluid (CSF) and orbit involvement occur in up to 20% of cases.Primary intraocular lymphoma predominates in the vitreous fluid and the retina.Beyond the orbit, PCNSL rarely disseminates systemically. Roughly 40% of systemic lymphomas arise in or near the CNS, including the paranasal sinuses and the previously mentioned localizations. Secondary CNS lymphoma preferentially affects the dura and leptomeninges; leptomeningeal metastases occur in 4% to 11% of patients with systemic lymphoma.

**Staging of Central Nervous System (CNS) Lymphoma**

* No Standard Staging System:  
  Unlike many other cancers, primary CNS lymphoma (PCNSL) does not have a universally accepted standard staging system. The disease is generally considered localized to the CNS (brain, spinal cord, eyes) unless proven otherwise.
* Purpose of Staging:  
  Staging in CNS lymphoma focuses on determining whether lymphoma is confined to the CNS or has spread outside it, such as to the eyes, cerebrospinal fluid (CSF), or systemic sites (lymph nodes, bone marrow).
* Common Staging Workup Includes:
  + Brain and spinal cord MRI with contrast to assess extent within CNS.
  + Ophthalmologic examination (slit lamp) to detect intraocular lymphoma.
  + CSF analysis via lumbar puncture for cytology and flow cytometry to detect lymphoma cells.
  + PET-CT or CT scans of chest, abdomen, pelvis to exclude systemic lymphoma.
  + Bone marrow biopsy if systemic involvement is suspected.
  + Blood tests to assess overall health and organ function.
* Clinical Staging Considerations:
  + PCNSL is often diagnosed when lymphoma is confined to the CNS without systemic disease.
  + Secondary CNS lymphoma refers to systemic lymphoma that has spread to the CNS and is staged as systemic lymphoma with CNS involvement.
  + About 60% of patients with CNS lymphoma present with advanced (stage IV) disease when systemic involvement is present.
* Lugano Classification:
  + The Lugano classification is the standard for systemic lymphoma staging but is not typically applied to PCNSL because PCNSL is confined to the CNS.
  + For systemic lymphoma with CNS involvement (secondary CNS lymphoma), Lugano staging is used.
* Recurrence and Monitoring:
  + PCNSL frequently recurs within the CNS after treatment, making ongoing surveillance critical.
  + Staging at recurrence involves repeat imaging and CSF/ocular assessment.

## **Doctor-Patient Conversation: CNS Lymphoma**

Doctor: Hello, I want to talk with you about your diagnosis of primary central nervous system lymphoma, or CNS lymphoma. How are you feeling today?

Patient: I’m quite anxious, doctor. What exactly is CNS lymphoma?

Doctor: CNS lymphoma is a type of cancer that starts in the lymphocytes, a kind of white blood cell, but it’s located in your brain, spinal cord, or eyes. It’s a rare but aggressive disease. The good news is that with prompt treatment, many patients respond well.

Patient: What tests will I need to understand the extent of the disease and plan treatment?

Doctor: We will do an MRI of your brain and spinal cord to see where the lymphoma is. You’ll also have an eye exam and a lumbar puncture to check the cerebrospinal fluid. To make sure the lymphoma hasn’t spread elsewhere, we’ll do PET or CT scans of your chest, abdomen, and pelvis, and possibly a bone marrow biopsy.

Patient: What treatments are available for this?

Doctor: The main treatment is chemotherapy with drugs that can cross into the brain, especially high-dose methotrexate. Often, we combine chemotherapy with immunotherapy using a drug called rituximab. Sometimes, radiation therapy to the whole brain is used, especially if chemotherapy alone isn’t enough. In some cases, stem cell transplant may be considered. We also have clinical trials offering newer targeted therapies.

Patient: What side effects should I expect from the treatment?

Doctor: Chemotherapy can cause side effects like fatigue, nausea, and lowered blood counts, which increase infection risk. Methotrexate can affect kidney and liver function, so we monitor you closely. Radiation can sometimes affect memory or thinking, especially in older patients. We provide supportive care to manage side effects throughout treatment.

Patient: What can I expect after treatment? Is there a chance the lymphoma will come back?

Doctor: Many patients achieve remission, but CNS lymphoma can relapse, so we’ll have regular follow-up visits with MRI scans and clinical assessments. If the lymphoma returns, there are additional treatments and clinical trials we can consider.

Patient: Will the lymphoma or its treatment affect my daily life or abilities?

Doctor: CNS lymphoma and its treatment can affect brain function, causing memory or coordination difficulties. Physical therapy and rehabilitation can help improve these issues. We have a multidisciplinary team to support you physically, mentally, and emotionally throughout your care.

Patient: Is there support available for me and my family?

Doctor: Absolutely. We have specialist nurses, counselors, and support groups to help you and your loved ones. We can also provide educational materials and information about clinical trials.

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

Even when CNS lymphoma goes into remission (no signs or symptoms of cancer), you’ll need regular check-ups to see if the cancer comes back. You’ll need more frequent visits within the first five years of treatment. Most CNS lymphoma that recurs comes back within the first five years.

#### **What questions should I ask my healthcare provider?**

## What tests will I need to determine my care plan?

* Brain MRI: To locate and characterize the lymphoma lesions in the CNS.
* Eye exam (ophthalmologic evaluation): To check for lymphoma involvement in the eyes.
* Lumbar puncture (spinal tap): To analyze cerebrospinal fluid (CSF) for lymphoma cells using cytology and flow cytometry.
* Biopsy: Brain or leptomeningeal biopsy is the gold standard to confirm diagnosis and subtype.
* PET-CT or CT scans: To detect lymphoma outside the CNS (systemic involvement).
* Bone marrow biopsy: To check for bone marrow involvement if systemic disease is suspected.
* Blood tests: To assess overall health and organ function.

These tests together help define the extent of disease and guide treatment decisions.

## 2. What are the risks and benefits associated with various treatment options?

* High-dose methotrexate-based chemotherapy: Mainstay treatment with good response rates; side effects include kidney and liver toxicity, nausea, fatigue, and lowered blood counts.
* Rituximab (immunotherapy): Often combined with chemotherapy; may increase effectiveness with manageable side effects.
* Whole-brain radiation therapy: Used in some cases; risks include cognitive decline and memory problems, especially in older patients.
* Stem cell transplant: Considered in recurrent or refractory cases; risks include infection and treatment-related toxicity.
* Palliative care: Focuses on symptom management and quality of life; no curative intent but important for supportive care.

Your healthcare team will discuss benefits and risks tailored to your age, overall health, and disease status.

## 3. How often will I need follow-up testing to see how the cancer responds to treatment?

* Initially, frequent monitoring with MRI scans and clinical exams every few weeks to months during and after treatment.
* CSF analysis may be repeated if initially positive.
* Over time, follow-up intervals usually extend to every 3–6 months for the first few years, then annually.
* Regular follow-up is critical because CNS lymphoma often recurs.

## 4. Am I eligible to enroll in a clinical trial? Would you recommend I do so?

* Eligibility depends on factors like your overall health, disease stage, prior treatments, and specific trial criteria.
* Clinical trials may offer access to newer therapies, such as targeted agents or novel immunotherapies.
* Your oncologist can help determine if any suitable trials are available and discuss potential benefits and risks.
* Participation in clinical trials is encouraged when appropriate, as it may improve outcomes and advance research.

## 5. Do you recommend palliative care?

* Palliative care is recommended to manage symptoms, improve quality of life, and provide psychosocial support throughout your illness.
* It can be provided alongside curative treatment or when treatment is no longer effective.
* Early integration of palliative care helps address pain, neurological symptoms, fatigue, and emotional needs

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## **Germ Cell Tumors**

Germ cell tumors that develop in the brain or spinal cord are also called CNS (central nervous system) germ cell tumors. Most germ cell tumors appear in the ovaries (ovarian tumors) or testes (testicular tumors), but they can also get “trapped” in the brain during the fetal period. They can be benign (noncancerous) or malignant (cancerous).

* The two main types of germ cell tumors of the brain are germinomas and non-germinomatous tumors. If they include aspects of both, they are called mixed germ cell tumors.
* Germ cell tumors of the brain are rare, accounting for approximately 4 percent of brain tumors in children.
* Around 50 percent occur in children between 10 to 15 years old.
* They are most commonly found in or around the pituitary and pineal glands.

### **Causes and Symptoms of Childhood Germ Cell Tumors of the Brain**

Researchers don’t know the cause of germ cell tumors. Usually, germ cells migrate to the gonads during fetal development. They become an egg in the female ovaries or sperm in the male testes. However, when these germ cells don't move to the right area, they can become trapped in the brain and multiply in areas where they shouldn't.

It's important to understand that these and other brain tumors most often occur with no known cause. There's nothing that you could have done or avoided doing that would have prevented the tumor from developing.

Symptoms typically depend on where they have developed in the brain. For tumors in the pineal gland region, children can have the following symptoms:

* Hydrocephalus (swelling of the brain)
* Headache
* Vomiting
* Fatigue
* Behavioral or cognitive changes
* Uncoordinated body movement (ataxia)
* Vision changes, including double vision and difficulty looking up

For tumors in the suprasellar or pituitary gland region, common symptoms include:

* Diabetes insipidus (an uncommon disorder characterized by intense thirst and the passing of large amounts of urine)
* Delayed puberty
* Early (precocious) puberty
* Stunted growth
* Vision changes, including loss of peripheral vision or decrease in vision

## **Diagnose and Classify Childhood Germ Cell Tumors of the Brain**

Effective treatment starts with an accurate diagnosis. Doctors typically confirm a diagnosis using a combination of physical and neurological exams, advanced imaging studies, blood tests, and lumbar puncture.

Successfully treating your child's germ cell tumor depends on identifying the tumor type and location. We classify germ cell tumors of the brain into two main types:

* **Germinomas**: These are pure germ cell tumors. They respond well to treatment.
* **Non-germinomatous tumors**: These tumors secrete chemicals into the spinal fluid and bloodstream. They require more intensive treatment than germinomas.
  + There are several sub-types of non-germinomatous germ cell tumors, including teratomas, choriocarcinomas, endodermal sinus tumors (yolk sac tumors), embryonal carcinomas, and mixed tumors.

After we complete all diagnostic testing, a team of pediatric tumor experts comes together to decide on the best treatment plan for your child. We meet with you and your family to discuss our treatment recommendations and answer any questions.

## **Treatment of Childhood Germ Cell Tumors of the Brain**

Your child's treatment plan will depend on their age, health, and medical history, as well as the tumor’s characteristics.

Treatments we offer include:

When a tumor causes blockage of cerebral spinal fluid flow, our surgeons may perform one of two procedures to relieve symptoms of hydrocephalus, the buildup of fluid inside the skull.

Tumors that are unlikely to spread receive radiation to the tumor and the area surrounding it. If the tumor is likely to spread beyond its original location, we may recommend radiation to other parts of the brain and spinal cord. If the tumor has already spread, we deliver radiation to the whole brain and spinal cord.

* **Surgery**: We initially use surgery to biopsy the tumor and form a complete diagnosis. Depending on the germ cell tumor type, we may recommend further surgery to remove as much of the tumor as possible.
  + **Endoscopic third ventriculostomy (ETV)**: In an endoscopic third ventriculostomy, surgeons create a small hole that allows fluid to flow around the blockage.
  + **Ventriculo-peritoneal shunt (VP shunt)**: In some cases, children may have an alternative procedure in which a tube is placed in the ventricles to the abdomen to drain excess fluid into the stomach.
* **Chemotherapy**: Chemotherapy treatment involves medications that interfere with a cancer cell’s ability to grow or reproduce. Doctors use it to shrink tumors and eliminate remaining cancer cells. Different groups of chemotherapy drugs work in different ways. They are generally systemic treatments. Your child may receive chemotherapy in the following ways:
  + Orally, as a pill to swallow
  + Intramuscularly, as an injection into the muscle or under the skin
  + Intravenously (IV), as a direct injection into the bloodstream
  + Intrathecally, as a direct injection into the spinal fluid
* **Radiation therapy**: Doctors may use radiation therapy, which involves using high-energy waves to shrink tumors or damage and destroy cancer cells.

## **Differential Diagnosis of Germ Cell Tumors (GCTs)**

1. Germinoma
   * Most common CNS GCT subtype.
   * Positive for markers like OCT4, PLAP, and c-kit.
   * Usually normal AFP, may have mildly elevated β-hCG.
2. Nongerminomatous Germ Cell Tumors (NGGCTs):
   * Teratoma: Mature, immature, or with malignant transformation.
   * Embryonal carcinoma: Aggressive, OCT4 and CD30 positive, AFP usually negative.
   * Yolk sac tumor: AFP positive, aggressive behavior.
   * Choriocarcinoma: β-hCG positive, highly malignant.
   * Mixed germ cell tumors: Contain two or more histologic types.
3. Other CNS Tumors Mimicking GCTs:
   * Pineal region tumors: Pineocytoma, pineoblastoma.
   * Colloid cysts: Benign cystic lesions in the third ventricle.
   * Metastatic tumors: From unknown primary sites, can mimic GCTs on imaging.
   * Cysticercosis: Parasitic infection causing cystic brain lesions.
   * Lymphoma: Primary CNS lymphoma can resemble GCT on imaging.
   * Astrocytomas and other gliomas: Especially in pediatric patients.
   * Craniopharyngioma: Suprasellar cystic tumor in children and young adults.
4. Inflammatory and Infectious Conditions:
   * Neurosarcoidosis or granulomatous inflammation mimicking germinoma histologically.
   * Infectious granulomas or abscesses.

## **Common Genetic Mutations and Pathways**

* KIT mutations:
  + Occur in approximately 21.5–33% of CNS GCTs, especially germinomas.
  + KIT encodes a tyrosine kinase receptor; mutations cause constitutive activation, driving tumor growth via downstream pathways.
* RAS gene mutations (KRAS, NRAS):
  + Present in about 10.8–20% of CNS GCTs, mutually exclusive with KIT mutations.
  + Activate the MAPK signaling pathway, promoting proliferation and survival.
* Other mutated genes:
  + CBL (5.2–11%), NF1 (3%), USP28 truncations, and amplifications of CRKL and KRAS via extrachromosomal DNA have been reported.
  + These mutations affect MAPK and PI3K/AKT/mTOR pathways, critical for tumorigenesis.

## 2. Chromosomal Alterations

* Chromosome 12p gain:
  + Found in about 30% of CNS GCTs, more frequent (~50%) in NGGCTs.
  + Considered an early event in tumor development and linked to worse prognosis.
* Other recurrent gains involve chromosomes 1q and 8q, while losses are seen in parts of chromosomes 11, 13, and 18.

## 3. Epigenetic and Transcriptomic Features

* DNA methylation:
  + Germinomas show global low DNA methylation, resembling primordial germ cells during migration, suggesting their cell of origin.
* Gene expression:
  + Germinomas overexpress immune-related genes (e.g., CCL18, CD72, IL6R) and immune checkpoint molecules like PD-L1, consistent with cytotoxic T-cell infiltration.
  + NGGCTs exhibit more immunosuppressive microenvironments with abundant macrophages and natural killer cells.

## 4. Molecular Subtypes

* Three molecular subtypes identified by transcriptomic analyses:
  + Immune-hot: Older onset, strong immune response, mostly germinomas.
  + MYC/E2F: Younger onset, genomic instability, germinomas.
  + SHH subtype: Mostly NGGCTs, associated with sonic hedgehog pathway alterations.

**Epidemiology of Central Nervous System (CNS) Germ Cell Tumors (GCTs)**

* Incidence:
  + CNS GCTs are rare, accounting for about 0.5% of all primary brain and CNS tumors.
  + In the United States, the incidence is approximately 0.07 to 0.10 per 100,000 person-years.
  + Around 90% of cases occur before age 20, predominantly affecting children and adolescents.
  + CNS GCTs represent about 3–5% of primary CNS tumors in children in Western countries.
* Age and Gender Distribution:
  + Most patients are adolescents and young adults, with a median age around 16 years.
  + There is a strong male predominance, especially for tumors in the pineal region, with a male-to-female ratio up to 15:1.
  + For tumors outside the pineal region (e.g., suprasellar), the gender ratio is closer to 1:1 or slightly favors females.
* Geographic and Ethnic Variation:
  + Historically, CNS GCT incidence has been higher in East Asia (Japan, Taiwan, China, Korea), where these tumors account for 7.8% to 14% of pediatric brain tumors, compared to about 4% in North America and Europe.
  + Recent data from Japan suggest incidence rates similar to those in the United States, indicating possible changes in reporting or environmental factors.
  + In the U.S., the incidence is 60% higher in Asian/Pacific Islanders compared to whites and non-Hispanics, and lowest in African Americans.
* Tumor Subtypes and Prognosis:
  + CNS GCTs are broadly classified into germinomas (about 60–70% of cases) and nongerminomatous germ cell tumors (NGGCTs).
  + Germinomas have an excellent prognosis with high cure rates due to their sensitivity to radiotherapy and chemotherapy.
  + NGGCTs are more heterogeneous, often more aggressive, and have a poorer prognosis.
* Survival:
  + The 5-year survival rate for CNS GCT patients is generally high, around 85–91%, with no significant differences based on sex or age group.

<https://emedicine.medscape.com/article/281714-overview>

**CUTANEOUS T-CELL LYMPHOMA**

**DEFINITION AND DESCRIPTION**

Cutaneous T-cell lymphoma is a rare type of cancer that begins in the white blood cells. The cancer affects white blood cells called T cells, also called T lymphocytes. These cells help the body's germ-fighting immune system. In cutaneous T-cell lymphoma, the T cells attack the skin.

Cutaneous T-cell lymphoma, also called CTCL, can cause rash and slightly raised or scaly round patches on the skin. Sometimes other growths appear on the skin.

There are several types of cutaneous T-cell lymphoma. The most common types include:

* **Mycosis fungoides.** Mycosis fungoides is the most common type of cutaneous T-cell lymphoma. It grows slowly. Mycosis fungoides mainly affect the skin. It often causes patches of affected skin.
* **Sezary syndrome.** Sezary syndrome is a less common type of cutaneous T-cell lymphoma. It grows and expands quickly. Sezary syndrome affects the skin and the blood. In time, it causes a rash over the whole body.

Treatment depends on the type of cutaneous T-cell lymphoma. Treatments can include skin creams, light therapy, radiation therapy and chemotherapy.

Cutaneous T-cell lymphoma is a type of non-Hodgkin lymphoma. Another type of non-Hodgkin lymphoma that affects the skin is called cutaneous B-cell lymphoma. Cutaneous T-cell lymphoma is much more common than cutaneous B-cell lymphoma.

**Causes**

The cause of cutaneous T-cell lymphoma often isn't known. This cancer causes a growth of cells in the skin. It starts in germ-fighting white blood cells called lymphocytes. Cutaneous T-cell lymphoma affects specific lymphocytes called T lymphocytes.

Cutaneous T-cell lymphoma happens when T lymphocytes develop changes in their DNA. A cell's DNA holds the instructions that tell the cell what to do.

DNA gives healthy cells 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 quickly. Cancer cells can keep living when healthy cells would die. This causes too many cells.

In cutaneous T-cell lymphoma, the cancer cells build up in the skin. In one type of cutaneous T-cell lymphoma called Sezary syndrome, the cancer cells also are in the blood.

**Risk factors**

The risk of cutaneous T-cell lymphoma may be higher in:

* **Older adults.** The condition can happen at any age, but it's more common in people 50 and older.
* **People assigned male at birth.** The condition is twice as common in people assigned male at birth than it is in people assigned female at birth.
* **Black people.** Black people have the highest risk of getting cutaneous T-cell lymphoma. Black people also are more likely to get this cancer at an earlier age.

There is no way to prevent cutaneous T-cell lymphoma.

**Symptoms**

Signs and symptoms of cutaneous T-cell lymphoma include:

* Patches of raised or scaly skin that might itch. The patches happen most often on skin that doesn't get much sun.
* Patches of skin that look pink, red, brown or gray. The color may be harder to see on Black and brown skin.
* Patches of skin that look lighter in color than the skin around them. This may be easier to see on Black and brown skin.
* Lumps that form on the skin and may break open.
* Lymph nodes that get bigger.
* Hair loss.
* Thickened skin on the palms of the hands and soles of the feet.
* A rash over all the skin that is scaly and itchy.

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

Make an appointment with a healthcare professional if you have symptoms that worry you.

## **Diagnosis**

To diagnose cutaneous T-cell lymphoma, a healthcare professional might start with an exam to look for signs of cancer. Tests and procedures might include blood tests, skin biopsies and imaging tests. Cutaneous T-cell lymphoma may be hard to diagnose because the symptoms are like those of other skin conditions, such as eczema. And early tests may not show cancer cells in the skin. Getting the right diagnosis may take time.

### **Physical exam**

A healthcare professional may do a physical exam to look over your skin for scaly areas or growths. The healthcare professional may check for other signs of cutaneous T-cell lymphoma, such as swollen lymph nodes.

### **Blood tests**

Blood tests such as a complete blood count can give information about your condition. Sometimes blood tests show cancer cells in the blood. This is more common with one type of cutaneous T-cell lymphoma called Sezary syndrome.

SKIN BIOPSY

A skin biopsy is a procedure to remove cells from the surface of the body so that they can be tested in a lab. The tests can show whether cancer cells are present in the skin.

A healthcare professional might take the sample of cells with a circular cutting tool. This type of biopsy is called a punch biopsy. For larger areas and growths, the healthcare professional might use a small knife. This is called an excisional biopsy.

Skin biopsies don't always detect cancer cells, even when cancer is present. You might need more than one skin biopsy over time.

### **Imaging tests**

If there's concern that the cancer cells have spread to other parts of the body, your healthcare professional might suggest imaging tests. These might include a computerized tomography scan, also called a CT scan, or a positron emission tomography scan, also called a PET scan.

**Treatment**

Treatments for cutaneous T-cell lymphoma include medicines, radiation therapy, light therapy and bone marrow transplant. Many treatments exist for this cancer. Your treatment plan may include a mix of treatments.

### **Skin creams and ointments**

Some medicines for cutaneous T-cell lymphoma are applied to the skin. The medicines may come in creams, gels and ointments.

Medicines used in this way include:

* **Steroid medicines.** Steroid medicines put on the skin can help control rash and itchiness.
* **Chemotherapy medicines.** Chemotherapy treats cancer with strong medicines. Some chemotherapy medicines are put on the skin to kill the cancer cells.

### **Light therapy**

Light therapy for cutaneous T-cell lymphoma involves shining a certain kind of light on the skin to kill the cancer cells. During this treatment, you stand in a treatment area while lamps shine on your skin. The treatment often is given a few times a week for several weeks.

Sometimes light therapy also uses medicine to make the cancer cells easier to hurt with the light. This is called photodynamic therapy.

### **Radiation therapy**

Radiation therapy treats cancer with powerful energy beams. For cutaneous T-cell lymphoma, the energy beams are most often X-rays or electrons. The treatment might target a small area of cancer on the skin. Or it can be given to all the skin on the body.

### **Medicines in pill form or through a vein**

Some medicines for cutaneous T-cell lymphoma are given in pill form or through a vein. Giving the medicine this way means it travels through the body and can treat the cancer wherever it is growing.

Medicines used in this way include:

* **Chemotherapy.** Chemotherapy treats cancer with strong medicines. The medicines kill the cancer cells.
* **Targeted therapy.** 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.
* **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.

### **Bone marrow transplant**

A bone marrow transplant, also called a bone marrow stem cell transplant, involves putting healthy bone marrow stem cells into the body. These cells replace cells hurt by chemotherapy and other treatments. A bone marrow transplant might be used when cutaneous T-cell lymphoma is far along or comes back after other treatments.

**Lifestyle and home remedies**

Many people with cutaneous T-cell lymphoma have itchy skin. Caring for your skin may help. Besides what your healthcare professional gives you to control itching, it also may help to:

* **Use mild soap with no scent.** This might help ease itching. When you wash your skin, use warm, not hot, water.
* **Keep skin moisturized.** Put a gentle lotion, cream or ointment with no scent on your skin after showers and baths. Use the moisturizer throughout the day as needed. This can help ease itching.

## **Outlook / Prognosis**

Most CTCLs grow very slowly and aren’t life-threatening. But some people develop serious forms of the condition. Healthcare providers can’t cure CTCLs, but they can successfully manage symptoms with treatment.

But like all cancers, CTCLs can be fatal in their advanced stages. The sooner you start treatment, the better. That’s why it’s so important to tell a provider whenever you notice changes in your skin.

#### **Survival rate for cutaneous T-cell lymphoma**

The overall 10-year survival rate for people with early-stage (Stage I or II) CTCL is 90%. That means that 9 out of 10 people with this condition are still alive 10 years later. People with late-stage CTCL (Stage III or IV) have an overall 10-year survival rate of 53%.

Survival rates are estimates. They can’t tell you how long you’ll live or how you’ll respond to treatment. To learn more about survival rates and what they mean for you, ask your healthcare provider.

## **Prevention**

Most people who have CTCL have no changeable risk factors. So, there’s nothing you can do to prevent it. But researchers continue to study why these conditions happen.

#### **How can I lower my risk?**

Even though you can’t prevent cutaneous T-cell lymphoma, a weakened immune system could make you more susceptible to CTCLs and all types of cancer. Here are some ideas for keeping your immune system strong:

* Eat lots of fruits and vegetables.
* Exercise regularly.
* Get enough good-quality sleep.
* Limit drinks containing alcohol.
* Maintain a weight that’s healthy for you.
* Manage stress with meditation or other mindfulness activities.
* Stay up to date on vaccines.
* Try to quit smoking.
* Wash your hands often.

## **Living With**

Cutaneous T-cell lymphoma affects your skin, making it dry, itchy and scaly. While treatment slows cancer growth and eases symptoms, some treatments may irritate already aggravated skin. Here are some suggestions that may help:

* Keep your skin moist. Use creams or ointments after you bathe or shower to lock in moisture and protect your skin. You may want to re-apply creams or ointments throughout your day and before you go to bed. In addition to protecting your skin, moisture combats dryness that makes your skin flake, helps with itchiness and may shield your skin from infection.
* Protect your skin from irritation. If you have cutaneous T-cell lymphoma, your skin is more vulnerable. Everyday activities like being in the sun, using certain laundry detergents and soaps or even wearing certain fabrics can irritate your skin. Look for fragrance-free detergents and body soaps. Wear clothing that protects your skin from the sun and use sunscreen when going outside. Wear loose-fitting clothes that let your skin breathe.
* Don’t scratch that itch. For many people, incessantly itchy skin is a serious issue affecting their quality of life. Scratching can break open your skin and allow bacteria to get inside. This can lead to infections. Cold compresses (think bags of frozen vegetables), oatmeal baths and antihistamines may help soothe itchy skin.

## **Epidemiology**

Cutaneous T-cell lymphoma has a worldwide distribution; some studies have identified a higher prevalence of the disease in industrial populations (eg, among workers who use machine cutting oils). The incidence of cutaneous T-cell lymphoma in the United States was reported to be 6.4 persons per million population annually (for the overall, age-adjusted incidence) between 1973 and 2002, with the disease’s incidence increasing over that time period.

Adult T-cell lymphoma/leukemia is endemic in areas with a high prevalence of HTLV-1 infection, such as southwest Japan, the Caribbean islands, South America, and parts of central Africa. This disease occurs in 1-5% of seropositive individuals after more than 2 decades of viral persistence.

Nasal-type NK/T-cell lymphoma, which is associated with Epstein-Barr virus (EBV) infection, is more common in Asia, Central America, and South America.

A study in Kuwait found that the annual incidence rate of mycosis fungoides there was 0.43 cases per 100,000 persons.

### Race-, sex-, and aged-related demographics

In the United States, cutaneous T-cell lymphoma is more common among persons of sub-Saharan African lineage than among those of European background, in a ratio of approximately 2:1. In Kuwait, a study found that the annual incidence rate of mycosis fungoides was significantly higher among Arabs than among non-Arab Asians.

Cutaneous T-cell lymphoma has a sex predilection, being more common in men than women by a ratio of approximately 2:1.

Most patients with cutaneous T-cell lymphoma are middle-aged or elderly. Sézary syndrome, for example, occurs almost exclusively in adults. Many patients have had a poorly defined form of dermatitis for many years prior to the onset of the disease. In a significant proportion of cases, the onset of the disease, or of a dermatitic precursor of the disease, occurs in childhood.

However, cutaneous T-cell lymphoma is exceedingly rare in children younger than 10 years, and in such cases it does not show a male predominance; one series even reported a strong female predilection. Similar to adult patients, most children present in stage IA or IB and have a good to excellent prognosis with treatment, although cases progressing to plaque, tumor-stage disease, and death have been reported.

Some patients with limited mycosis fungoides are described as having Woringer-Kolopp disease (pagetoid reticulosis). These patients are usually middle-aged, with an age distribution in one series ranging from 13-68 years and with a mean age of 55 years.

## **Diagnostic Considerations**

Cutaneous T-cell lymphomas are T-cell proliferative disorders. Primary cutaneous lymphomas require distinction from histologically similar primary nodal ones because their clinical behavior, prognosis, and therapy are often different. In addition, a difference often exists between primary cutaneous and nodal lymphomas in the presence of specific translocations.

At times, disseminated infections such as leishmaniasis, leprosy, South American blastomycosis, coccidioidomycosis, and other deep fungal infections may mimic and require distinction from cutaneous T-cell lymphoma. Acne vulgaris, epidermal inclusion cysts, and insect bites may resemble folliculotropic mycosis fungoides.

Granulomatous mycosis fungoides with hypohidrosis may mimic lepromatous leprosy.Other conditions to consider in the differential diagnosis of cutaneous t-cell lymphoma include non lymphomatous erythroderma and erythema neurolyticum migrans.

## **Differential Diagnoses**

* Allergic Contact Dermatitis
* Irritant Contact Dermatitis
* Lichen Planus
* Parapsoriasis
* Pediatric Atopic Dermatitis
* Pemphigus Foliaceus
* Plaque Psoriasis
* Pustular Psoriasis
* Tinea Corporis

## **Key Genetic Alterations**

* Somatic Copy Number Variants (SCNVs):
  + SCNVs comprise about 92% of driver mutations in CTCL, with an average of ~12 pathogenic SCNVs per tumor, far exceeding single nucleotide variants (SNVs).
  + These include deletions and amplifications affecting key genes.
* Recurrently Mutated Genes:
  + Only a few genes are mutated in >10% of CTCL cases:
    - CDKN2A/B (tumor suppressors)
    - PCLO (involved in synaptic vesicle trafficking)
    - FAT1 (cadherin family, tumor suppressor)
    - TP53 (guardian of the genome, frequently mutated/deleted)
  + Other implicated genes affect T-cell activation, apoptosis, NF-κB signaling, chromatin remodeling, DNA damage response, JAK/STAT, and MAPK pathways.
* Mutational Signatures:
  + A prominent UV-induced mutational signature (signature 7) is found in mycosis fungoides (MF) and Sézary syndrome (SS), indicating UV exposure contributes to mutagenesis in skin-resident malignant T cells.
  + Age-related and other mutational signatures are also present.
* Structural Variants and Translocations:
  + Frequent intragenic translocations affecting genes like BACH2 uncouple coding sequences from promoters, altering gene expression.
  + Increased structural variants are seen in leukemic CTCL (Sézary syndrome) compared to early-stage MF.

## 2. Pathways Affected

* T-cell activation and NF-κB signaling: Key in lymphoma cell survival and proliferation.
* JAK/STAT signaling: Frequently dysregulated, promoting growth and immune evasion.
* MAPK signaling: Mutations affecting this pathway contribute to oncogenesis.
* Epigenetic regulators: Mutations in chromatin remodeling genes affect gene expression patterns.

## 3. Impact of Specific Mutations

* TP53:
  + Loss-of-function mutations and deletions are common, especially in advanced disease, correlating with poor prognosis.
* PD1 (Programmed cell death protein 1):
  + Deletions lead to reversal of T-cell exhaustion, aggressive disease, and worse outcomes.
* HAVCR2 (TIM-3):
  + Germline mutations identified in subcutaneous panniculitis-like T-cell lymphoma (SPTCL), a CTCL subtype, affecting immune checkpoint regulation.

**Cutaneous T-cell Lymphoma (CTCL): Procedures and Timeline**

## 1. Initial Evaluation and Diagnosis

* Physical Examination:
  + Thorough skin exam to identify patches, plaques, tumors, and check for lymphadenopathy.
  + Assessment of symptom history and extent of skin involvement.
* Skin Biopsy:
  + Punch biopsy for small lesions or suspicious patches.
  + Excisional biopsy for larger or nodular lesions.
  + Multiple biopsies over time may be needed due to the patchy nature of CTCL.
  + Histopathology and immunohistochemistry to confirm malignant T-cell infiltration.
* Blood Tests:
  + Complete blood count (CBC) with differential to detect circulating malignant T cells (Sézary cells).
  + Flow cytometry to identify abnormal T-cell populations.
  + Liver and kidney function tests, lactate dehydrogenase (LDH), and uric acid levels to assess disease burden and organ function.
  + Testing for HIV and HTLV-1 in some cases.
* Molecular Studies:
  + T-cell receptor (TCR) gene rearrangement studies (PCR or Southern blot) to detect clonal T-cell populations.
* Imaging:
  + CT or PET scans to evaluate lymph node involvement or visceral disease, especially in advanced stages.
* Lymph Node Biopsy:
  + If lymphadenopathy is present, biopsy to assess nodal involvement.

## 2. Staging

* Based on TNMB system (Tumor, Node, Metastasis, Blood):
  + Stages I to IV, depending on skin involvement, lymph node status, blood involvement, and visceral metastases.
  + Staging guides prognosis and treatment decisions.

## 3. Treatment Timeline

* Early Stage (I-II):
  + Skin-directed therapies (topical corticosteroids, phototherapy, topical chemotherapy).
  + Treatment duration varies; response assessed every few months.
  + Regular follow-up every 3–6 months.
* Advanced Stage (III-IV) or Blood Involvement (Sézary Syndrome):
  + Systemic therapies (retinoids, interferons, histone deacetylase inhibitors, chemotherapy, monoclonal antibodies).
  + Treatment cycles typically every 3–4 weeks; ongoing until disease control or toxicity.
  + Close monitoring with blood tests and imaging every 2–3 months initially.

## 4. Follow-Up and Monitoring

* Regular skin exams and symptom assessment at each visit.
* Repeat biopsies if new or changing lesions appear.
* Periodic blood tests and imaging to monitor disease progression or response.
* Frequency of visits depends on disease stage and treatment response, typically every 3–6 months for stable disease.

## **QUESTION AND ANSWER SET**

## What's likely causing my symptoms?

CTCL is a type of cancer that starts in T-lymphocytes (a kind of white blood cell) that normally help fight infections. In CTCL, these malignant T cells accumulate in the skin, causing symptoms like itchy, dry, red, or scaly patches and plaques. The itch can be intense, especially in advanced stages or in Sézary syndrome, a more aggressive form of CTCL. Other symptoms can include weight loss, fever, chills, and fatigue, but not everyone experiences these.

## 2. Other than the most likely cause, what are other possible causes for my symptoms?

Many benign skin conditions can mimic CTCL symptoms, such as:

* Eczema or atopic dermatitis
* Psoriasis
* Allergic contact dermatitis
* Lichen planus
* Parapsoriasis
* Other inflammatory or infectious skin disorders

Because CTCL can look like these common skin diseases, multiple biopsies and tests may be needed to confirm the diagnosis.

## 3. What tests do I need?

* Skin biopsy: To examine skin tissue under a microscope for cancer cells. Multiple biopsies may be needed.
* Blood tests: To check for malignant T cells in the blood (especially in Sézary syndrome) and assess overall health.
* Flow cytometry and molecular studies: To detect abnormal T-cell populations and T-cell receptor clonality.
* Imaging (CT, PET scans): To assess lymph node or internal organ involvement if advanced disease is suspected.
* Lymph node or bone marrow biopsy: If systemic involvement is suspected.

## 4. What's the best course of action?

Treatment depends on the type and stage of CTCL:

* Early-stage disease: Skin-directed therapies such as topical corticosteroids, phototherapy (UV light), topical chemotherapy, or radiation.
* Advanced-stage or blood involvement: Systemic treatments including oral retinoids, interferons, histone deacetylase inhibitors, chemotherapy, monoclonal antibodies, or extracorporeal photopheresis.
* Clinical trials: New therapies are continually being studied; ask your doctor about eligibility.

## 5. I have other health conditions. How can I best manage them together?

Managing CTCL alongside other health conditions requires coordinated care:

* Inform your healthcare providers about all your conditions and medications.
* Some CTCL treatments may affect liver, kidney, or immune function, so monitoring is essential.
* Your doctor may adjust CTCL treatment to minimize interactions or side effects.
* Supportive care for symptoms like itching and skin infections is important.
* Regular follow-up helps balance CTCL management with other health needs.

## 6. Are there restrictions I need to follow?

* Avoid excessive sun exposure unless directed for phototherapy.
* Maintain good skin care to prevent infections and dryness.
* Follow treatment plans closely and report new or worsening symptoms.
* Some systemic therapies may require avoiding live vaccines or certain medications.
* Discuss lifestyle modifications with your healthcare team, including diet, stress management, and infection prevention.

## 7. Should I see a specialist?

Yes. CTCL is a complex disease that benefits from care by specialists such as:

* Dermatologists experienced in cutaneous lymphomas.
* Hematologist-oncologists specializing in lymphomas.
* Multidisciplinary teams at specialized centers provide the best outcomes.
* Early referral to a specialist ensures accurate diagnosis, staging, and access to advanced treatments and clinical trials

## **Doctor-Patient Conversation: Cutaneous T-cell Lymphoma (CTCL)**

Doctor: Hello, I want to discuss your recent diagnosis of cutaneous T-cell lymphoma, or CTCL. How are you feeling about this news?

Patient: I’m quite worried and confused. What exactly is CTCL?

Doctor: CTCL is a type of cancer that starts in a kind of white blood cell called T-lymphocytes, which normally help your immune system. In CTCL, these cells become abnormal and accumulate in the skin, causing rashes, patches, or plaques that can be itchy or scaly. It’s a rare but treatable condition.

Patient: What tests did you do to confirm this?

Doctor: We took a skin biopsy, which means a small piece of your skin was examined under the microscope. We also did blood tests to check if the abnormal cells are in your blood, and imaging tests to see if lymph nodes or other organs are involved. Sometimes, multiple biopsies are needed because CTCL can look like other skin conditions.

Patient: What treatment options do I have?

Doctor: Treatment depends on the stage and extent of your disease. For early-stage CTCL, we often start with skin-directed therapies such as topical steroids, phototherapy (light treatment), or topical chemotherapy. If the disease is more advanced or involves the blood, we may use systemic treatments like oral medications, immunotherapy, or targeted therapies. Our goal is to control symptoms and maintain your quality of life.

Patient: Are there side effects I should be concerned about?

Doctor: Each treatment has potential side effects. For example, phototherapy can increase skin sensitivity, and systemic treatments may cause fatigue or affect your immune system. We will monitor you closely and manage side effects proactively.

Patient: How often will I need follow-up?

Doctor: Regular follow-up is important. Initially, we’ll see you every few months to monitor your skin and overall health, adjust treatment if needed, and perform repeat tests if your symptoms change.

Patient: Should I see any specialists?

Doctor: Yes, it’s best to be managed by a dermatologist and oncologist experienced in CTCL. They work together with a multidisciplinary team to provide comprehensive care. We can refer you to a specialized center if needed.

Patient: Can I continue my daily activities? Are there any restrictions?

Doctor: Most patients can continue their usual activities. It’s important to care for your skin, avoid irritants, and protect yourself from excessive sun exposure unless phototherapy is part of your treatment. We’ll guide you on any specific precautions.

Patient: Is CTCL contagious? Can I pass it to my family?

Doctor: No, CTCL is not contagious. It cannot be passed from person to person.

Patient: What support is available for me?

Doctor: You’ll have access to nurses, counselors, and patient support groups. We encourage you to involve family or friends for emotional support. We can also provide written information and resources to help you understand your condition better.

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### **Mycosis fungoides**

Mycosis fungoides (pronounced “my-KOH-sis fun-GOY-deez”) is a blood cancer that happens when white blood cells called T cells transform into malignant (cancer) cells. T cells are a kind of lymphocyte. Lymphocytes fight harmful pathogens in your body, like viruses and bacteria. With mycosis fungoides, T cells transform into cancer cells that affect your skin.

Mycosis fungoides is a type of cutaneous T-cell lymphoma (CTCL). CTCL is a group of rare blood cancers that cause changes in your skin, like itchiness, rashes, plaques or tumors.

Although mycosis fungoides affect your skin, it’s not a form of skin cancer because your T cells — not skin cells — become cancerous.

## **Symptoms and Causes**

Mycosis fungoides symptoms occur in several stages of skin changes. Not everyone progresses through all the phases. Some may happen simultaneously.

For many people, the first sign of disease in the early stage is a mycosis fungoides rash. Mycosis fungoides stages include:

* Premycotic phase: A scaly skin rash forms. It appears on parts of your body not usually exposed to the sun, like your lower belly, thighs, butt and breasts (chest).
* Patch phase: The skin around the rash becomes thin. It may be itchy and dry, like eczema.
* Plaque phase: Your skin forms small, raised bumps or hard bumps.
* Tumor phase: Tumors, raised areas of skin that penetrate more deeply than plaques, form on your skin. The most common locations include your thighs, groin, armpits and the inside of your elbow. The tumors may develop ulcers and get infected.

In the most severe stages, many cancerous T cells circulate in your blood. At this point, they’re called Sézary cells. High levels of Sézary cells may cause mycosis fungoides to evolve into Sézary syndrome. With this condition, you may develop a red rash all over your body, called erythroderma.

### **What causes mycosis fungoides?**

Experts don’t know what causes mycosis fungoides, but genetic mutations may play a role. Genetic mutations are changes in the genetic material inside a cell, like DNA or chromosomes. Many people with mycosis fungoides have missing genetic material or errors in the genetic material inside the cells that become malignant.

These genetic mutations don’t seem to be inherited (passed down through families).

Researchers continue to study other potential causes, such as exposure to certain environmental toxins and infections.

#### **Is mycosis fungoides contagious?**

Mycosis fungoides aren't contagious. It doesn’t spread from person to person.

## **Diagnosis and Tests**

It may be challenging to diagnose mycosis fungoides based on a visual skin exam because it can resemble other skin conditions. It’s easy to mistake mycosis fungoides for more common skin conditions during an exam, like eczema or psoriasis.

To confirm or rule out mycosis fungoides, your healthcare provider will likely perform additional tests such as:

* Skin biopsy or lymph node biopsy: A procedure that removes tissue from the affected area so a pathologist can test the tissue in a lab for signs of mycosis fungoides. You may need multiple biopsies to locate evidence of the tumor cells associated with mycosis fungoides.
* Blood tests: Your healthcare provider may look for changes in your blood cells and chemical markers (like enzymes) that may be signs of mycosis fungoides.
* Imaging procedures: Your healthcare provider may look for signs that the cancer has spread to your lymph nodes or organs other than your skin. Imaging procedures may include a CT scan or PET scan.

### **How do doctors stage mycosis fungoides?**

Cancer staging is an important part of a mycosis fungoides diagnosis. Cancer staging classifies mycosis fungoides on a scale from I to IV based on how invasive it is and the extent it’s spread. Knowing the stage helps your healthcare provider determine treatments.

Stages IA through IIB are regarded as early-stage mycosis fungoides. Stages IIB through IVB are considered advanced disease.

When staging mycosis fungoides, providers consider various factors, including:

* The size of skin lesions (patches, plaques and tumors).
* How much of your skin contains skin lesions.
* Whether the cancer has spread to your lymph nodes.
* Whether the cancer has spread to your bloodstream.
* Whether the cancer has spread to organs other than your skin.

## **Management and Treatment**

Mycosis fungoides treatment depends on the cancer stage and type of skin changes. Many treatment options focus on relieving symptoms and improving your quality of life.

Your healthcare provider may prescribe:

* Skin-directed therapy: Topical gels, steroids, retinoids or ultraviolet (UV) light (phototherapy) treat cancer on affected areas of your skin. With psoralen-ultraviolet A therapy (PUVA), a healthcare provider combines a pill (psoralens) with UV light to destroy cancer cells on your skin. Your provider may also use a topical chemotherapy drug, such as mechlorethamine (Valchlor®).
* Systemic therapy: Medicines such as bexarotene (Targretin®) or methotrexate (Rheumatrex®, Trexall®) can treat your whole body. Other classes of drugs include Interferon α and histone deacetylase (HDAC) inhibitors. Intravenous medicines (taken through your vein) include chemotherapy, such as gemcitabine (Gemzar®), pegylated liposomal doxorubicin or pralatrexate (Folotyn®).
* Immunotherapy: Immunotherapy boosts your immune system so it’s better at identifying and attacking cancer cells.
* Monoclonal antibodies as targeted therapy: These medicines detect and destroy cancer cells. Healthcare providers may use targeted therapy if your body hasn’t responded to other systemic therapy. Treatments include mogamulizumab-kpkc (POTELIGEO®) and brentuximab vedotin (Adcetris®).
* Radiation therapy: With radiation therapy, strong beams of energy from outside your body destroy cancer cells or stop their growth.

Healthcare providers rarely use traditional chemotherapy for mycosis fungoides. Chemotherapy doesn’t always effectively treat mycosis fungoides. It also carries a significant risk of side effects.

### **Is there a cure for mycosis fungoides?**

There isn’t a cure for mycosis fungoides. Although there’s no way to get rid of it completely, with early diagnosis and treatment, people often live for many years without symptoms. Most live a normal life span.

## **Outlook / Prognosis**

Your prognosis depends on multiple factors, with cancer stage being especially important.

It’s much easier to treat mycosis fungoides in its early stages. Many people who receive early diagnosis and treatment experience long periods with no symptoms.

More advanced mycosis fungoides may need more intensive treatment. For example, you may need radiation therapy or chemotherapy if cancer has spread beyond your skin.

### **What is the life expectancy of someone with mycosis fungoides?**

The 10-year survival rate for early-stage mycosis fungoides is 95%. The life expectancy for advanced mycosis fungoides is three to five years, and it may be less if the cancer has spread beyond your skin.

Still, it’s important to remember that these numbers are just statistics. Your prognosis depends on various factors unique to you, including age, overall health and disease course. Your healthcare provider is your best resource for answering questions about what to expect with mycosis fungoides, including likely treatment outcomes and life expectancy.

## **Prevention**

There’s no proven way to prevent mycosis fungoides. You can reduce the risks of late-stage mycosis fungoides by scheduling regular appointments with a healthcare provider. Regular checkups can increase the chances of detecting mycosis fungoides in its early stages.

Perform monthly skin self-checks for rashes, moles or other changes. If you notice any skin changes, schedule an appointment with a dermatologist.

## **Differential Diagnosis of Mycosis Fungoides (MF)**

* Sezary Syndrome (leukemic CTCL variant with erythroderma and circulating malignant T cells)
* Eczema (Atopic Dermatitis)
* Psoriasis
* Pityriasis Rubra Pilaris
* Contact Dermatitis (allergic and irritant)
* Chronic Actinic Dermatitis
* Scabies
* Adult T-cell Leukemia/Lymphoma
* Hypereosinophilic Syndrome
* Subcutaneous Panniculitis-like T-cell Lymphoma (SPTCL)
* Drug Eruption
* Graft versus Host Disease
* Lichen Planus
* Pediatric Atopic Dermatitis
* Tinea Corporis (Fungal Infection)
* Primary Cutaneous Anaplastic Large Cell Lymphoma (ALCL)
* Cutaneous Gamma/Delta T-cell Lymphoma
* Pityriasis Lichenoides Chronica
* Nummular Dermatitis
* Secondary Syphilis
* Bowen’s Disease
* Exanthematous Pustulosis
* Hypertrophic Lichen Planus
* Sneddon–Wilkinson Disease
* Small Plaque Parapsoriasis
* Intertrigo
* Langerhans Cell Histiocytosis
* Tinea Manuum/Pedum/Capitis
* Seborrheic Dermatitis
* Dermatomyositis (especially poikilodermatous MF variant)
* Lupus Erythematosus (subacute or chronic cutaneous)
* Bullous Autoimmune Diseases (e.g., pemphigus, bullous pemphigoid)
* Folliculitis and Pustular Psoriasis (MF variants can mimic these)
* Granulomatous Mycosis Fungoides (may mimic granuloma annulare, sarcoidosis, leprosy)
* Granulomatous Slack Skin Syndrome
* Erythema Annulare Centrifugum and Other Figurate Erythemas (in annular MF)
* Erythema Gyratum Repens (rare annular MF mimic)

**Epidemiology of Mycosis Fungoides (MF)**

* Incidence and Prevalence:
  + MF is the most common cutaneous T-cell lymphoma (CTCL), accounting for approximately 40–65% of all CTCL cases and about 50% of primary cutaneous lymphomas.
  + The annual incidence ranges from about 0.3 to 0.6 cases per 100,000 people in the US and UK, with some variation:
    - US SEER data estimate incidence around 0.29 to 0.38 per 100,000.
    - UK incidence reported as approximately 3.7 per million (0.37 per 100,000).
  + Prevalence estimates in the US range from 5.2 to 6.6 per 100,000 people.
* Age Distribution:
  + MF predominantly affects adults and the elderly, with a median age at diagnosis of 55–60 years.
  + Although rare, MF can also occur in children and adolescents, with delayed diagnosis common in pediatric cases.
  + Incidence increases with age, being highest among the elderly.
* Gender:
  + There is a consistent male predominance, with a male-to-female ratio of approximately 2:1 across multiple studies.
* Ethnic and Geographic Variation:
  + MF is slightly more common in Black populations compared to Whites, and less common in Asians and Hispanics.
  + Geographic variation exists, with higher incidence reported in some regions, possibly related to environmental or occupational exposures.
  + Occupational risk factors include farming, painting, woodworking, textiles, petrochemicals, and metal industries.
* Trends Over Time:
  + Incidence of MF has increased over the past decades, possibly due to earlier diagnosis and improved detection methods rather than a true increase in disease occurrence.
  + Survival rates have improved, likely reflecting earlier diagnosis and advances in treatment.
* Survival:
  + MF generally has a favorable prognosis, especially in early-stage disease, with a 5-year survival rate between 79% and 92%.
  + Most patients are diagnosed at early stages, though data on early-stage prevalence is limited

**STAGING**

**Skin**

* T1: Limited patches, papules, and/or plaquescovering less than 10% of the skin surface. May further stratify into T1a (patch only) vs. T1b (plaque +/- patch).
* T2: Patches, papules or plaques covering 10% or more of the skin surface. May further stratify into T2a (patch only) vs. T2b (plaque +/- patch).
* T3: One or more tumors(1 cm or more in diameter)
* T4: Confluence of erythema covering 80% or more of body surface area

**Lymph Nodes**

N0: No clinically abnormal peripheral lymph nodes; biopsy not required

N1: Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN0-2

* N1a: Clone negative (A T-cell clone is defined by PCR or Southern blot analysis of the T-cell receptor gene)
* N1b: Clone positive

N2: Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3

* N2a: Clone negative
* N2b: Clone positive

N3: Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3 to 4 or NCI LN4; clone positive or negative

Nx: Clinically abnormal peripheral lymph nodes; no histologic confirmation

**Visceral**

M0: No visceral organ involvement

M1: Visceral involvement (must have pathology confirmation and organ involved should be specified)

**Blood**

B0: Absence of significant blood involvement: 5% or less of peripheral blood lymphocytes are atypical (Sezary) cells

* B0a: Clone negative
* B0b: Clone positive

B1: Low blood tumor burden: more than 5% of peripheral blood lymphocytes are atypical (Sezary) cells but does not meet the criteria of B2

* B1a: Clone negative
* B1b: Clone positive

B2: High blood tumor burden: 1000/microL or more Sezary cells with positive clone

## **Doctor-Patient Conversation: Mycosis Fungoides**

Doctor: Hello, I want to talk with you about your diagnosis of mycosis fungoides, which is a type of cutaneous T-cell lymphoma. How are you feeling about this?

Patient: Honestly, I’m quite worried. I don’t really understand what this means. What exactly is mycosis fungoides?

Doctor: Mycosis fungoides is a rare type of cancer that starts in certain immune cells called T-lymphocytes, which normally help protect your body. In this disease, these cells become abnormal and accumulate mainly in the skin, causing patches or plaques that can be itchy or scaly. It often looks like eczema or psoriasis at first, which can make diagnosis tricky.

Patient: What tests did you do to confirm this?

Doctor: We performed a skin biopsy, which involves taking a small sample of your skin to look at under the microscope. Sometimes, multiple biopsies are needed because the disease can be patchy. We also did blood tests to check if the lymphoma cells are in your bloodstream and imaging to see if lymph nodes or other organs are affected.

Patient: What treatment options do I have? Will I have to be on treatment forever?

Doctor: Treatment depends on the stage of your disease. For early-stage mycosis fungoides, we usually start with skin-directed therapies like topical steroids, phototherapy (UV light treatment), or topical chemotherapy agents such as nitrogen mustard. These treatments can control symptoms and sometimes lead to remission. Many patients manage their disease with these therapies for years. If the disease progresses, we have other systemic treatments available.

Patient: Are there side effects I should be worried about?

Doctor: Each treatment has potential side effects. For example, phototherapy can make your skin more sensitive to sunlight. Topical treatments may cause irritation. Systemic treatments can have more side effects, but we monitor you closely to manage any issues. Also, because your skin barrier is compromised, you may be more prone to skin infections, so gentle skin care is very important.

Patient: How often will I need to come in for check-ups?

Doctor: Initially, we’ll see you every few months to monitor your skin and response to treatment. Over time, if your disease is stable, visits may be spaced out. We also recommend you report any new or worsening symptoms promptly.

Patient: Should I see any specialists?

Doctor: Yes, it’s best to be followed by a dermatologist experienced in cutaneous lymphomas, and often a hematologist-oncologist. They work together to provide comprehensive care and access to the latest treatments and clinical trials.

Patient: Can I continue my normal activities? Are there any restrictions?

Doctor: Most patients continue their daily activities. It’s important to take good care of your skin, avoid harsh soaps or irritants, and protect your skin from excessive sun exposure unless you are undergoing phototherapy. We’ll guide you on specific precautions.

Patient: Is this contagious? Can I pass it to my family?

Doctor: No, mycosis fungoides is not contagious. It cannot be passed from person to person.

Patient: What support is available for me?

Doctor: You’ll have access to nursing support, counseling, and patient support group

### **What questions should I ask my doctor?**

### **How common is mycosis fungoides?**

Mycosis fungoides are rare. Healthcare providers diagnose around 3,000 people with cutaneous T-cell lymphomas each year. On average, about 70% of all cutaneous T-cell lymphomas are mycosis fungoides. Because mycosis fungoides progresses slowly, more people may have the condition without knowing it.

Mycosis fungoides can affect people of all ages, but it’s most common in adults over 50. Males are twice as likely to develop mycosis fungoides. People who are Black are more likely to develop this condition than people who are white.

### **What is the difference between mycosis fungoides and Sézary syndrome?**

Mycosis fungoides occurs when T-cell lymphocytes become cancerous. When these cancerous T-cells circulate in your blood, they’re called Sézary cells.

Sézary syndrome occurs when you have large numbers of T-cells — called Sézary cells — in your blood that can go to your skin and lymph nodes.

### **What triggers mycosis fungoides?**

Scientists haven’t identified a single cause that triggers mycosis fungoides. They’ve identified common changes in specific chromosomes, including missing genetic material and genetic material with errors, within the cancer cells. These changes develop over a person’s lifetime (acquired).

### **What do mycosis fungoides look like on the skin?**

One of the challenges of diagnosing mycosis fungoides is that it doesn’t look the same on everyone. Also, in the early stages, it often resembles common skin conditions, like eczema and psoriasis.

Depending on the stage, it may look like a rash, raised and discolored skin or bumps that may develop sores. Most often, these skin changes occur on your body in places protected from sun exposure.

## Are there any side effects of mycosis fungoides treatment?

Yes, treatments for MF can cause side effects, which vary depending on the therapy used:

* Topical therapies (corticosteroids, nitrogen mustard, retinoids):
  + Skin irritation, redness, itching, allergic contact dermatitis, hyperpigmentation, and, rarely, secondary skin cancers.
  + Nitrogen mustard can cause allergic reactions and atypical skin changes.
* Phototherapy (PUVA, UVB):
  + Acute: skin redness, itching, nausea (from psoralens in PUVA), photosensitivity.
  + Long-term: increased risk of skin aging and secondary skin cancers.
* Systemic treatments (retinoids, interferons, chemotherapy, monoclonal antibodies like mogamulizumab):
  + Fatigue, nausea, hair thinning, infections due to immune suppression, infusion reactions (e.g., chills, rash, fever with mogamulizumab), blood count abnormalities.
  + Some systemic agents may cause depression, dry skin, muscle pain, or other organ toxicities.
* Radiation therapy:
  + Skin redness, dryness, peeling, and potential long-term skin changes.

## 2. What’s the risk that mycosis fungoides will return after treatment?

* MF is a chronic, often relapsing disease. Even after successful treatment and remission, MF can recur in the skin or, less commonly, in other organs like the spleen or liver.
* Recurrence risk depends on disease stage and treatment response; early-stage MF has a better prognosis with longer remission periods.
* Regular follow-up is important to detect and manage recurrences promptly.

## 3. What happens if I decide not to treat it?

* MF typically progresses slowly, especially in early stages, and may resemble benign skin conditions for years.
* Without treatment, skin lesions may worsen, thicken, and spread, potentially progressing to more advanced stages involving lymph nodes or internal organs.
* Symptoms like itching and skin discomfort may increase, and quality of life can decline.
* Advanced MF has a worse prognosis and may require more intensive treatment later.
* Early treatment generally improves symptom control and may delay progression.

## 4. How can I lower my chances that mycosis fungoides will return?

* Adhere to your treatment plan and attend all follow-up appointments for monitoring.
* Practice good skin care to maintain skin barrier health and prevent infections.
* Avoid skin irritants and excessive sun exposure (unless phototherapy is prescribed).
* Report new or changing skin lesions promptly to your healthcare provider.
* Maintain a healthy lifestyle to support your immune system.
* Some evidence suggests early diagnosis and treatment improve long-term control.

## 5. What resources are available for me to care for myself during treatment?

* Healthcare team support: Dermatologists, oncologists, nurses, and pharmacists provide education, symptom management, and treatment guidance.
* Patient education materials: From cancer centers and lymphoma foundations explaining disease, treatments, and skin care.
* Support groups: Both in-person and online communities for emotional support and shared experiences.
* Skin care guidance: Gentle cleansers, moisturizers, and avoidance of irritants recommended to reduce skin symptoms.
* Psychosocial support: Counseling services to help manage stress, anxiety, or depression related to chronic illness.
* Clinical trials: Access to new therapies through research studies if eligible.

REFERENCES

[Mycosis Fungoides: Symptoms and Treatment](https://my.clevelandclinic.org/health/diseases/21827-mycosis-fungoides#overview)

<https://www.ncbi.nlm.nih.gov/books/NBK519572/#article-25428.s10>

<https://www.cancer.gov/types/lymphoma/patient/mycosis-fungoides-treatment-pdq>

### **Sézary syndrome**

Sézary syndrome is a rare, fast-growing form of cutaneous T-cell lymphoma, a form of lymphoma that affects your skin. In Sézary syndrome, you have cancerous T lymphocytes (T-cells) in your skin, bloodstream and lymph nodes. The condition makes your skin change color, making it look red or darker than usual. It also causes a painful, itchy rash. The cancerous cells in your bloodstream may travel to other areas of your body. Healthcare providers have many ways to ease your symptoms, but there’s no cure for Sézary syndrome.

It’s rare, affecting about 1 in 1 million people in the United States annually.

## **Symptoms and Causes**

In Sézary syndrome, the most noticeable sign is a distinctive red rash (erythroderma) that itches a lot, hurts, peels and spreads quickly. (People of color may have patches of dark-colored skin that may look gray, purple or brown). Early on, Sézary syndrome symptoms look like eczema or psoriasis.

As Sézary syndrome gets worse, you develop small, raised bumps on your skin (papules). You may notice areas on your skin that feel harder or thicker than nearby skin (plaque). Eventually, you may develop tumors on your skin. Other signs and symptoms may include:

* Swollen lymph nodes.
* Fever.
* Fatigue.
* Unexplained weight loss.
* Hair loss.
* Eyelids that turn outward (ectropion).
* Enlarged liver (hepatomegaly).
* Swelling (edema) in your lower legs.
* Cold intolerance, where you feel cold even when in room temperature conditions.

### **What causes Sézary syndrome?**

Sézary syndrome happens when genetic mutations turn healthy T-cells into abnormal cells that multiply uncontrollably and eventually overpopulate the skin, lymph nodes and bloodstream. Experts aren’t sure what triggers the mutation.

#### **Risk factors**

Being infected with human T-cell leukemia virus (HTLV) may increase your risk of developing Sézary syndrome.

### **Complications of Sézary syndrome**

Sézary syndrome can affect your quality of life, making it hard to sleep and making you feel depressed or anxious. Other complications include:

* Cancerous T-cells spreading to your lungs, liver, spleen and bone marrow.
* Increased risk of another type of lymphoma.
* Increased risk of infections.

## **Diagnosis and Tests**

Your healthcare provider will do a physical examination and evaluate your symptoms. They’ll ask about your medical history. If they think you have Sézary syndrome, they may do the following tests:

* Blood tests, including a complete blood count (CBC) with differential, which includes checking the percentages of different white blood cells, a Sézary blood count to check the number of Sézary cells in your blood and a peripheral blood smear.
* Your provider may do biopsies of your skin, lymph nodes or bone marrow.
* A medical pathologist will study blood and tissue samples under a microscope. They’ll look for tumor markers and other changes in your cells that tell them more about what's going on.
* If blood tests and lab tests show you have Sézary syndrome, your provider may perform tests to see if the cancer has spread. Tests may include chest X-ray, CT scans and positron emission tomography (PET) scan.

## **Management and Treatment**

Your healthcare provider will recommend treatments based on your symptoms and the cancer stage. Treatments may include:

* Phototherapy: Providers may treat the condition with extracorporeal photopheresis, which involves collecting your white blood cells (leukapheresis) and exposing the cells to ultraviolet (UV) light. They may also use photopheresis or UV phototherapy.
* Radiation therapy: Treatment may include external radiation therapy or total skin electron beam radiation therapy.
* Chemotherapy: Providers may use topical chemotherapy that’s applied to your skin or systemic chemotherapy that affects your whole body. Vorinostat (Zolinza®) is an example of a systemic chemotherapy treatment.
* Targeted therapy: Monoclonal antibody therapy is an example of targeted therapy for Sézary syndrome.
* Immunotherapy: Providers may treat the condition with interferon (Intron A®, Intron A Multidose Pen.®).
* Other drug therapies: Corticosteroids, retinoid creams or gels like bexarotene (Targretin®) are other possible treatments.

#### **Treatment side effects**

Most cancer treatments have side effects. Common chemotherapy and radiation therapy side effects include fatigue, nausea and vomiting. Phototherapy may affect your skin. Targeted therapy, immunomodulators and immunotherapy may cause diarrhea, rash and fatigue, and blood count abnormalities.

## **Outlook / Prognosis**

Unfortunately, there’s no cure for Sézary syndrome. But some treatments can help manage symptoms, keep abnormal cells from dividing and multiplying, and slow down how fast the cancer spreads.

#### **How long does Sézary syndrome last?**

Sézary syndrome is a chronic disease, meaning you’ll need treatment for the rest of your life.

#### **What are Sézary syndrome survival rates?**

About 24% of people with Sézary syndrome survive for at least five years after the disease develops. This rate will improve as new, more effective treatments appear. When you think about survival rates, remember, they’re estimates based on other people’s experiences.

Sézary syndrome is rare, making it difficult to gather enough information. If you have questions about your situation, ask your healthcare provider what you can expect.

## **Living With**

Living with Sézary syndrome means receiving treatment for the rest of your life. You may need to take extra steps to protect your skin, like avoiding exposure to sunlight.

## **Differential Diagnosis of Sézary Syndrome:**

1. Classical Mycosis Fungoides (MF):
   * While MF is the most common form of CTCL and SS is a variant, they have distinct immunophenotypic profiles . MF typically involves patches and plaques that may progress to SS in some cases, suggesting a spectrum of disease . SS is defined by having malignant T-cells in the blood, which is not characteristic of early-stage MF .
2. Other Forms of Primary Cutaneous T-cell Lymphoma (CTCL):
   * This includes less common variants of CTCL that may have skin involvement but lack the characteristic leukemic features of SS, such as Folliculotropic MF, Granulomatous Slack Skin, and Pagetoid Reticulosis .
3. Causes of Erythroderma:
   * Psoriasis: Can cause widespread redness and scaling; however, psoriatic lesions typically have silvery scales and distinct histological features, and lack Sézary cells in the blood .
   * Atopic Dermatitis: Chronic inflammatory skin condition with widespread eczema, but typically without the specific T-cell clonality or Sézary cells found in SS .
   * Pityriasis Rubra Pilaris (PRP): A chronic inflammatory skin disorder characterized by orange-red plaques and follicular papules that can coalesce into erythroderma, but without malignant T-cell infiltration or Sézary cells .
   * Adverse Drug Reactions (Drug Eruptions): Can cause widespread skin redness and other systemic symptoms, but are typically acute and resolve upon discontinuation of the causative drug .
   * Dermatitis: Various forms of dermatitis can lead to widespread skin inflammation .
   * Hypereosinophilic Syndrome: Characterized by persistent eosinophilia and organ involvement, which can include skin manifestations that may resemble CTCL, but distinct hematologic and systemic features .
4. Other Skin Disorders:
   * Scabies: An intensely itchy parasitic infestation that can cause widespread rash, but identifiable burrows and mites are present .
   * Graft-versus-Host Disease (GVHD): An immune reaction in transplant recipients that can cause skin rashes, but occurs in the context of transplantation .
5. Adult T-cell Leukemia/Lymphoma (ATLL):
   * A rare and aggressive T-cell lymphoma associated with Human T-lymphotropic virus type 1 (HTLV-1) infection. It can present with skin lesions, lymphadenopathy, and circulating malignant cells, similar to SS, but differs in its association with HTLV-1 and specific immunophenotype .

## **Diagnostic Criteria for Sézary Syndrome:**

Diagnosis of SS requires the presence of erythroderma, generalized lymphadenopathy, and specific findings in the peripheral blood :

* Sézary cells: More than 1,000 Sézary cells/µL in the peripheral blood smear .
* Immunophenotypic abnormalities:
  + CD4/CD8 ratio of 10 or greater .
  + CD4+CD7- T cells greater than 40% .
  + CD4+CD26- T cells greater than 30%

Epidemiology of Sézary Syndrome (SS)

* Incidence:
  + Sézary syndrome is a rare and aggressive form of cutaneous T-cell lymphoma (CTCL).
  + The annual incidence is estimated at approximately 0.1 to 0.4 cases per 100,000 people (1 to 4 per million) in Europe and North America.
  + Some sources estimate around 30–40 new cases per year in the United States.
  + Incidence has been increasing over recent decades, likely due to improved recognition and diagnosis.
* Prevalence:
  + Population-wide studies (e.g., Finland) report a diagnosed prevalence rising from 0.16 to 0.36 per 100,000 between 1998 and 2016.
* Age and Gender:
  + SS predominantly affects older adults, with a median age at diagnosis between 60 and 65 years.
  + There is a male predominance, with men affected more frequently than women.
* Ethnic and Geographic Variation:
  + Data suggest higher incidence in white populations, reflecting study demographics, but black patients may present younger and with more aggressive disease.
  + Geographic variation exists but is limited by rarity and heterogeneous reporting.
* Relation to Mycosis Fungoides (MF):
  + SS represents about 3–5% of all cutaneous lymphomas and is considered a leukemic variant of MF.
  + Incidence of SS is much lower than MF but shows similar increasing trends.

**Genomic Data of Sézary Syndrome (SS)**

## 1. Somatic Mutations and Driver Genes

* Multiple somatic point mutations have been identified in genes involved in T-cell receptor signaling, tumorigenesis, and immune regulation, including:
  + ITPR1, ITPR2, DSC1, RIPK2, IL6, RAG2
  + Genes affecting T-cell receptor pathways and tumor suppression such as CBLB, RASA2, BCL7C, RAMP3, TBRG4, DAD1.
* Recurrent loss-of-function mutations target epigenetic regulators and chromatin remodeling genes:
  + ARID1A (40% of cases), members of the SMARC/ARID family, histone methyltransferases (MLLs, SETD1A/B), demethylases (KDM6B), DNA methyltransferases, and TET family genes.
* Frequent mutations also affect tumor suppressors and cell cycle regulators:
  + TP53, CDKN2A, PTEN, CDKN1B, RB1.

## 2. Copy Number Variations (CNVs) and Structural Variations

* Common chromosomal abnormalities include:
  + Deletions and duplications on chromosome 17, including loss of 17p.
  + Aneuploidies such as trisomy 8, monosomy 10, and other chromosomal instabilities.
* Numerous fusion genes have been discovered, including:
  + TPR-MET, MYBL1-TOX, DNAJC15-ZMYM2, EZH2-FOXP1, as well as fusions involving RASA2, NFKB2, BCR, FASN, ZEB1, TYK2, SGMS1.
  + These fusion events may contribute to oncogenesis and represent potential therapeutic targets.

## 3. Pathway Alterations

* The JAK/STAT pathway is frequently mutated, with gain-of-function mutations in JAK1, JAK3, STAT3, STAT5B (~11% of cases), suggesting sensitivity to JAK inhibitors.
* Mutations disrupt epigenetic regulation, cell cycle control, and immune signaling, driving malignant T-cell proliferation and survival.

## 4. Mutation Burden and Origin

* SS cells show a high mutational burden, with hundreds of mutations per genome.
* Recent studies indicate that mutations are present even in hematopoietic stem cells (CD34+ progenitors), suggesting early origin of malignant clones.

**Sézary Syndrome: Procedures and Timeline**

## 1. Initial Clinical Evaluation

* Physical Examination:
  + Detailed skin exam to assess extent of erythroderma (redness covering >80% body surface).
  + Check for lymphadenopathy (enlarged lymph nodes).
  + Review symptoms such as itching, skin thickening, and systemic signs.
* Medical History:
  + Document symptom onset, progression, prior skin conditions, treatments, and overall health.

## 2. Diagnostic Testing

* Skin Biopsy:
  + Multiple biopsies may be needed due to patchy involvement.
  + Histopathology looks for atypical malignant T cells with epidermotropism.
* Blood Tests:
  + Complete blood count (CBC) with differential to assess for Sézary cells.
  + Sézary cell count: Microscopic examination of blood to quantify circulating malignant T cells.
  + Flow cytometry: Immunophenotyping of blood T cells for markers such as CD2, CD3, CD4, CD5, CD7, CD8, CD26, and TRBC1 to detect abnormal populations (e.g., CD4+CD7- or CD4+CD26-).
  + T-cell receptor (TCR) gene rearrangement studies to confirm clonality in blood and skin.
* Lymph Node Biopsy:
  + If lymphadenopathy is present, biopsy to assess nodal involvement.
* Imaging Studies:
  + CT, PET, or MRI scans to evaluate lymph nodes and visceral organ involvement.
* Additional Tests:
  + HIV and HTLV-1 serologies may be performed to exclude viral-associated lymphomas.

## 3. Staging

* Based on TNMB system (Tumor, Node, Metastasis, Blood), staging guides prognosis and treatment.
* Stages range from early skin involvement to widespread erythroderma with blood and nodal disease.

## 4. Treatment Initiation and Monitoring

* Treatment typically starts after diagnosis and staging, tailored to disease extent.
* Common therapies include skin-directed treatments, systemic agents, photopheresis, and immunotherapies.
* Response to treatment is monitored clinically and via repeat blood tests and biopsies.

## 5. Follow-Up and Long-Term Management

* Regular follow-up visits every few months initially, then spaced out based on disease control.
* Repeat skin biopsies and blood tests to monitor disease progression or remission.
* Imaging repeated as clinically indicated.

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

Sézary syndrome symptoms may develop and change quickly. You should contact your provider if:

* You see changes in your skin, like redness or darker-colored skin spreading to more areas of your skin, or small bumps becoming larger. These symptoms may mean your condition is getting worse.
* You have frequent infections that take a long time to go away.

### **What questions should I ask my healthcare provider?**

### **What’s the difference between mycosis fungoides and Sézary syndrome?**

Mycosis fungoides is another type of cutaneous T-cell lymphoma. It affects your skin, causing a red or dark-colored rash. Unlike in Sézary syndrome, people with mycosis fungoides don’t have significant numbers of cancer cells circulating in their bloodstream. But mycosis fungoides may eventually turn into Sézary syndrome.

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**OPTIC NERVE GLIOMA**

**DEFINITION AND DESCRIPTION**

Optic nerve glioma is a slow-growing tumor, which typically affects children. 30% of patients have associated NF1 & those have better prognosis.

Malignant gliomas (glioblastoma) are rare & almost always occur in adult males with a very poor prognosis & almost certain death within one year. Optic-nerve gliomas Comprise about 1% of all intracranial tumors.

About 10% of optic pathway tumors are located within an optic nerve. One third of the tumors involve both optic nerve and chiasm, a further third involve predominantly the chiasm itself, and one fourth is predominantly in the hypothalamus. 5 5% gliomas are multicentric.

## **Diagnostic Procedures**

### **Computer Tomography (CT) scans**

Bone window setting on CT often reveals widening of the optic canal. In patients with associated NF1, there is typically a fusiform enlargement of the optic nerve with a clear cut margin produced by intact dural sheath. In patients without NF1 the nerve may be more irregular and have some low-density areas.

### **Magnetic resonance imaging (MRI) scans**

MRI often reveals enlargement, kinking, and buckling of the optic nerve. The nerve becomes enlarged and fusiform in shape because of attachment of the investing dura to the periosteum of the optic canal. On T2-weighted images, optic-nerve glioma is hyperintense to the cerebral cortex and may appear heterogeneous secondary to cystic degeneration. Gliomas enhance variably and a complete lack of enhancement can also occur. MRI may show cystic degeneration if present.

MRI is useful in showing intracranial extension. It is more sensitive for displaying chiasmatic/ hypothalamic tumors than CT. These tumors are usually hypointense on T1-weighted images and hyperintense on T2 as mentioned and almost always, enhanced with gadolinium. On T2, high intensity signals may be seen extending to the lateral geniculate bodies.

## **Differential diagnosis**

The major differential diagnostic considerations when an enlarged optic nerve is identified on imaging are inflammatory (neuritis, infection, or pseudotumor), neoplastic, or the result of increased intracranial pressure. Distinguishing inflammatory from neoplastic processes of the nerves is difficult because both may demonstrate optic-nerve enlargement with or without contrast enhancement. Clinical history can then be used to determine the underlying cause. Unilateral involvement, no pain on extraocular movement, no systemic inflammatory signs at around the onset of visual loss, no additional white-matter abnormality or recurrent visual symptoms during follow-up period might support a diagnosis of optic-nerve glioma rather than optic neuritis in childhood. Other tumorous conditions such as lymphoma or inflammatory pseudotumor may be ruled in the absence of a history of painful ophthalmoplegia or a rapid deterioration of symptoms during follow-up.

### **Optic nerve glioma**

* Hemangioma, Lymphoma, Rhabdomyosarcoma, Metastases (Neuroblastoma,
* Leukemia, Ewing’s sarcoma), Fibrous dysplasia, Paranasal mucocoele, Meningioma, Neurofibromatosis

### **Optic nerve and chiasm glioma**

* Germinoma, Sarcoidosis

### **Optic chiasm glioma extending into the hypothalamus**

* Pituitary adenoma, Craniopharyngioma, Malignant astrocytoma
* Dermoid cyst, Chordoma, Colloid cyst, Fibrous dysplasia, Sarcoidosis, Histiocytosis X, Tuberculous granuloma, Hemangioendothelioma

## **Optic glioma associated with neurofibromatosis type 1**

Neurofibromatosis type 1 (NF1) is an autosomal dominantly inherited disorder with an approximate incidence of 1:4,000. Optic glioma, one of the most significant complications of NF1 in childhood, developed with an approximate prevalence of 15% (range, 1.5–24%). The period of greatest risk for the development of symptomatic optic gliomas in NF1 is during the first 6 years of life.

# **Management**

## **Treatment**

The treatment of optic nerve gliomas is controversial. No treatment may be required in patients with no growth, good vision & no cosmetic deformity.

In case of malignant gliomas (glioblastomas) despite treatment, including high-dose radiotherapy and chemotherapy, these tumors usually result in death within 6-12 months.

There are rare reports of spontaneous regression of optic nerve and visual pathway gliomas. Cystic enlargement of the lesions associated with sudden visual loss can occur even without true cellular growth. A treatment plan must be carefully individualized for each patient.

The following options may be considered:

1. Observation only in presumed optic nerve glioma, particularly with good vision on the involved side; with careful follow up if the radiographic evidence is characteristic of this type of tumor and if the glioma is confined to the orbit. Follow-up examinations and appropriate radiographic studies, preferably MRI, must be performed at regular intervals. Many patients maintain good vision and never require surgery.
2. Surgical excision in case of rapid intraorbital tumor growth to isolate the tumor from the optic chiasm and thus prevent chiasmal invasion. The surgeon should use an intracranial approach to obtain tumor-free surgical margins. Additional surgical indications may include tumors confined to the orbit with corneal exposure and compromised cosmesis unacceptable to the patient. Removal through an intracranial approach may also be indicated at the time of initial diagnosis or after a short period of observation if the tumor involves the prechiasmal intracranial portion of the optic nerve. Complete excision is possible if the tumor ends 2-3 mm anterior to the chiasm. Excision may also be required if the glioma causes an increase in intracranial pressure. Excision is rarely utilized in cases where there is residual vision.
3. Radiation therapy as the sole treatment is considered if the tumor cannot be resected (usually chiasmal or optic tract lesions) and if symptoms (particularly neurological) progress. Postoperative radiation of the chiasm and optic tract may also be considered if good radiographic studies document subsequent growth of the tumor within the chiasm or if chiasmal and optic tract involvement is extensive.
   * Because of debilitating side effects (including mental retardation, growth retardation, optic neuropathy or retinopathy, and secondary tumors within the radiation field), radiation is generally held as a last resort for children who have not completed growth and development.
4. Combination chemotherapy using actinomycin D, vincristine, etoposide, bevacizumab and other agents has also been reported to be effective in patients with progressive chiasmal/hypothalamic gliomas. Chemotherapy may delay the need for radiation therapy and thus enhance long-term intellectual development and preservation of endocrine function in children. However, chemotherapy may also carry long-term risks of blood-borne cancers.
   * Regression of optic gliomas has been reported after partial resection, chemotherapy, radiotherapy, or biopsy, and sometimes without any treatment. Other variables such as genetic, hormonal, or vascular factors seem to have more influence on tumor behavior. Most spontaneous regressions of optic glioma have been reported in those with NF1.

**DIFFERENTIAL DIAGNOSIS**

* Optic Nerve Sheath Meningioma
* Optic Neuritis (inflammatory demyelination)
* Orbital Pseudotumor (Idiopathic Orbital Inflammation)
* Orbital Lymphoma
* Metastases (e.g., neuroblastoma, leukemia, Ewing’s sarcoma)
* Rhabdomyosarcoma
* Fibrous Dysplasia
* Paranasal Sinus Mucocele
* Neurofibromatosis Type 1 (NF1)-associated optic pathway glioma
* Perioptic Hemorrhage
* Erdheim-Chester Disease
* Juvenile Xanthogranuloma
* Medulloepithelioma
* Retinoblastoma
* Krabbe Disease
* Germinoma (optic nerve and chiasm glioma)
* Sarcoidosis (optic nerve and chiasm involvement)
* Pituitary Adenoma (optic chiasm glioma extension)
* Craniopharyngioma
* Malignant Astrocytoma
* Dermoid Cyst
* Chordoma
* Colloid Cyst
* Histiocytosis X
* Tuberculous Granuloma
* Hemangioendothelioma

**EPIDEMIOLOGY**

Optic pathway gliomas primarily affect children aged 10 and younger, constituting 3% to 5% of childhood central nervous system (CNS) tumors. However, these gliomas can occur across a wide age range, from birth to 79. Notably, 71% of cases occur within the first decade of life, and 90% are diagnosed within the first 2 decades. The mean age at which optic gliomas are diagnosed is approximately 8.8. In patients with NF1, approximately 15% to 20% eventually develop optic pathway gliomas, although only 30% to 50% of those individuals experience symptoms. The incidence of NF1 in patients presenting with optic nerve gliomas varies widely, ranging from 10% to 70%, with an overall incidence of 29%.

Men and women are generally affected equally by optic pathway gliomas. However, with gliomas confined to the optic nerve, an increased incidence in women (65%) compared to men (35%) is common. Conversely, when tumors involve the optic chiasm, men and women are affected equally. At presentation, gliomas are confined to the optic nerve in 25% of cases, while 75% of cases show chiasm involvement.Additionally, when the chiasm is involved, 40% of patients develop an extension of the tumor to the hypothalamus or third ventricle.

**Optic Nerve Glioma (ONG) Treatment Drugs and Their Side Effects**

## 1. Standard Chemotherapy

* Vincristine and Carboplatin (First-line treatment)
  + Purpose: Shrinks tumor and stabilizes or improves vision, especially in children.
  + Side Effects:
    - Vincristine: Peripheral neuropathy (numbness, tingling), constipation, hair loss, jaw pain.
    - Carboplatin: Bone marrow suppression (low blood counts), nausea, vomiting, kidney toxicity, allergic reactions.
  + Notes: Standard chemotherapy remains the mainstay despite modest visual outcomes.
* Vinorelbine (Monotherapy)
  + Used in progressive cases with promising progression-free survival rates.
  + Side effects similar to vincristine but generally better tolerated.

## 2. Molecularly Targeted Therapies

* MEK Inhibitors (e.g., Selumetinib, Trametinib, Binimetinib, Cobimetinib, Refametinib)
  + Purpose: Target MAPK pathway mutations in low-grade gliomas, including ONG.
  + Efficacy: Selumetinib showed ~69% 2-year progression-free survival and visual stability or improvement in many patients.
  + Side Effects: Rash, diarrhea, fatigue, elevated liver enzymes, cardiac effects, eye toxicity (retinopathy).
  + Notes: Approved for selected pediatric low-grade gliomas; ongoing clinical studies.
* Bevacizumab (Anti-VEGF antibody)
  + Used experimentally to reduce tumor vascularity and growth.
  + Side effects include hypertension, bleeding risk, proteinuria, impaired wound healing.

## 3. Radiation Therapy

* Conventional Radiation Therapy
  + Used for unresectable tumors or progressive disease after chemotherapy.
  + Side effects: Skin irritation, fatigue, risk of secondary malignancies, damage to developing brain tissue in children.
* Stereotactic Radiosurgery (SRS) and Fractionated Stereotactic Radiotherapy (SRT)
  + Highly focused radiation minimizing damage to surrounding tissue.
  + Side effects similar to conventional radiation but generally better tolerated.

## 4. Surgical Treatment

* Surgery is generally reserved for:
  + Rapid tumor growth causing mass effect or increased intracranial pressure.
  + Tumors confined to the orbit with corneal exposure or cosmetic issues.
* Surgery risks include vision loss, damage to optic pathways, and neurological deficits.

## 5. Supportive Medications

* Corticosteroids
  + Used to reduce peritumoral edema and intracranial pressure.
  + Side effects: Weight gain, immunosuppression, mood changes, hyperglycemia

## **Genomic and Molecular Characteristics:**

* NF1 gene mutations are central to the pathogenesis of optic pathway gliomas in NF1 patients. NF1 encodes neurofibromin, a tumor suppressor that regulates RAS signaling. Loss or mutation of NF1 leads to increased RAS activity, promoting tumor growth.
* Specific germline NF1 mutations can differentially influence tumor development and growth. For example, the R681X mutation in NF1 is associated with larger and more proliferative optic gliomas in mouse models compared to other mutations.
* Microglia, the brain’s immune cells, contribute to tumor maintenance by producing growth factors such as the chemokine CCL5, which supports glioma proliferation. Targeting microglia or their secreted factors can reduce tumor growth in experimental models.
* Neurofibromin deficiency in retinal ganglion cells (RGCs) leads to decreased cAMP levels, increased apoptosis, and vision loss. Pharmacologic elevation of cAMP can protect RGCs and preserve vision in mouse models

**DOCTOR PATIENT CONVERSATION**

Doctor: "Your child has been diagnosed with an optic nerve glioma, which is a type of benign, slow-growing tumor affecting the optic nerve. These tumors most often occur in children and can cause symptoms like blurred vision or mild eye protrusion."

Patient/Parent: "Is this cancer? How serious is it?"

Doctor: "Optic nerve gliomas are generally not cancerous in the traditional sense—they are low-grade tumors. They tend to grow slowly and can often be managed effectively. However, because the tumor affects the optic nerve, it can impact vision, so our goal is to preserve as much vision as possible."

Patient/Parent: "What treatments are available?"

Doctor: "Treatment depends on symptoms and tumor progression. We usually start with chemotherapy, which can help shrink the tumor or stop its growth and stabilize vision. If chemotherapy is not effective or if the tumor progresses, radiation therapy is another option. Surgery is rarely done because it carries a high risk of vision loss, but it may be considered in severe cases."

Patient/Parent: "What about side effects or long-term outlook?"

Doctor: "Side effects vary depending on treatment, but we carefully tailor therapy to minimize risks. For example, advanced radiation techniques can target the tumor while sparing healthy tissue. After treatment, your child will need regular follow-up with MRI scans and vision exams to monitor for any changes. Many children do well with treatment, but lifelong monitoring is important."

Patient/Parent: "Will this affect my child's daily life?"

Doctor: "We aim to maintain your child's quality of life. We have support services for children with vision challenges and programs to help with school and physical therapy if needed. Our team will work closely with you throughout treatment and beyond."

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[Optic Nerve Glioma - EyeWiki](https://eyewiki.org/Optic_Nerve_Glioma)

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### **Teratoma**

A teratoma is a type of germ cell tumor — a tumor that starts in your reproductive cells like eggs and sperm. Most teratomas are benign (noncancerous), but sometimes they can become malignant (cancerous).

Germ cells are the only cells in your body that can turn into many other types of cells. So, when a tumor starts in your germ cells, it can turn into many different types of tissue. This means teratomas can contain fragments of any body part. Some of the most common structures inside a teratoma include:

* Teeth.
* Hair.
* Fat.
* Muscle.

Less commonly, teratomas can even contain remnants of complex body parts like:

* Liver.
* Lungs.
* Brain.
* Thyroid gland.

It’s even possible to have one with eyes — at least parts of them, including eyeballs. But to date, there’s no record of a teratoma with complete body organs.

#### **Types of teratomas**

Healthcare providers categorize teratomas into two main types:

* Mature teratomas are usually noncancerous (benign tumors). Mature teratomas can occur at any age, but they’re most common during your reproductive years.
* Immature teratomas are cancerous. They’re most common among children.

Teratomas can form anywhere in your body. Some examples include:

* Ovarian teratomas. These are the most common type in [females](https://my.clevelandclinic.org/health/articles/sex-recorded-at-birth). Most ovarian teratomas are cystic teratomas (filled with fluid, tissue or other materials). A very small percentage of them are cancerous. Most are benign.
* Testicular teratomas. These are the most common type in males. In boys, these tumors are usually non cancerous. But in men, they’re malignant in over half of the cases.
* Sacrococcygeal teratomas. These are the most common types in children. But they’re still rare overall, occurring in about 1 in 40,000 live births. This tumor develops near the coccyx (tailbone) and is more common among females.

##### **Fetiform teratomas**

The rarest type of teratoma tumor, a fetiform teratoma occurs in about 1 in 500,000 people. It’s a type of dermoid cyst that consists of living tissue and often resembles a malformed fetus. But because there’s no placenta or amniotic sac, the fetus has no chance of development. In about 90% of cases, healthcare providers diagnose fetiform teratomas within the first 18 months of life.

A fetiform teratoma resembles a parasitic twin (fetus in fetu). Fetus in fetu only occurs in twins who both share the same placenta and have their own sac of amniotic fluid.

## **Symptoms and Causes**

People with teratomas may not show any symptoms at first. Once symptoms develop, they can vary significantly depending on the tumor’s location. General teratoma symptoms may include:

* Pain.
* Bleeding.
* Swelling.
* Slightly elevated levels of the hormone BhCG (beta-human chorionic gonadotropin).
* Slightly elevated levels of tumor marker AFP (alpha-fetoprotein).

But you may also develop specific additional symptoms based on the location of the teratoma tumor.

#### **Ovarian teratoma symptoms**

Main symptoms of ovarian teratomas include:

* Abdominal pain.
* Pelvic pain (this happens when the tumor places excess pressure on your ovary).

In some instances, ovarian teratomas may occur alongside NMDA encephalitis — a rare condition that can lead to severe headaches, confusion and psychosis.

#### **Testicular teratoma symptoms**

Primary symptoms of testicular teratomas include:

* Lump in your testicle.
* Swelling in one or both testicles.

In some cases, people with testicular teratomas may not show any symptoms.

#### **Sacrococcygeal teratoma symptoms**

Sacrococcygeal teratomas can form inside or outside your body in the tailbone (coccyx) area. Possible symptoms include:

* Tailbone pain (coccydynia).
* A visible mass in your tailbone area.
* Abdominal pain.
* Constipation.
* Painful urination (dysuria).
* Swelling in your pubic area.
* Weakness in your legs.

### **What causes a teratoma?**

A teratoma develops when there are disruptions during your cells’ differentiation process. It’s sort of like cell differentiation in an embryo: Unspecialized cells (cells that don’t have a specific function yet) turn into specialized cells with a specific purpose (like blood cells, nerve cells and muscle cells).

In the case of a teratoma, your unspecialized germ cells turn into different types of specialized cells (like hair cells, muscle cells and bone cells). That’s why a teratoma contains a collection of seemingly random body parts and tissues.

### **Complications of a teratoma**

Specific complications vary based on the location of the teratoma. But in general, teratoma complications may include:

* Torsion (a body part twists and causes pain).
* Rupture (a tumor bursts or breaks open).
* Infection.
* Cancerous transformation (a tumor that started as noncancerous turns cancerous).

## **Diagnosis and Tests**

A healthcare provider will do a physical examination and ask about your symptoms and medical history. They may also recommend tests to confirm a diagnosis.

These tests may include:

* Imaging tests like X-rays, CT (computed tomography) scans, magnetic resonance imaging (MRI) and ultrasound to determine the size and location of the teratoma.
* Blood tests to check hormone levels and measure tumor markers.
* Biopsy to find out if the teratoma is cancerous or noncancerous.

With the development of imaging technology, healthcare providers can sometimes diagnose a teratoma during pregnancy.

## **Management and Treatment**

Typically, the first step is surgery to remove the teratoma. Nearly all teratomas require removal when discovered. Even if they aren’t cancerous, they can still grow or rupture, leading to other issues.

If your teratoma is cancerous, your healthcare provider may also recommend:

* Chemotherapy.
* Radiation therapy.
* Chemoradiation (chemotherapy and radiation therapy).

## **Outlook / Prognosis**

The vast majority of teratomas are noncancerous. In most cases, these tumors don’t spread like aggressive cancers. As a result, most teratomas — even cancerous ones — have excellent survival rates with early diagnosis and treatment.

## **Prevention**

Currently, there’s no known way to prevent teratomas. But early treatment can greatly reduce your risk for complications.

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

Anytime you notice a new lump or bump on your skin or persistent abdominal pain, you should schedule a visit with a healthcare provider. They can run appropriate tests and give you a diagnosis.

If you already know you have a teratoma, or had surgery to remove one, you should call your provider if you develop pain or other new symptoms.

**DIFFERENTIAL DIagnosis**

* Intracranial lipoma
  + Contains only fatty tissue; homogeneous fat density on imaging without calcifications.
* Intracranial dermoid cyst
  + Contains more mature tissues; may rupture causing chemical meningitis; usually midline.
* Craniopharyngioma
  + Typically suprasellar; cystic and solid parts; calcifications common; different embryonic origin.
* Other pineal region tumors
  + Includes germinomas, pineocytomas, pineoblastoma; germinomas often have elevated AFP or β-hCG.
* Low-grade gliomas
  + Solid tumors without fat or calcification; different molecular profiles.
* Primitive neuroectodermal tumors (PNET)
  + Highly malignant pediatric tumors; lack fat or cystic components typical of teratomas.
* Ependymoma
  + Usually intraventricular or spinal; can mimic teratomas on imaging.
* Langerhans cell histiocytosis
  + Can involve CNS; systemic signs and different histology.
* Metastatic lesions
  + Usually multiple lesions; clinical history of primary tumor.
* Neural tube defects (for sacrococcygeal teratomas)
  + Meningocele or meningomyelocele.

**EPIDEMIOLOGY**

Cystic teratomas are the most common ovarian germ cell tumors comprising 20% of all the ovarian tumors in adults and half of all ovarian neoplasms in children and are usually benign. On the contrary, malignancy is a rare occurrence constituting about 1%. They are most predominant in women in their second and third decades of life as the most common benign tumor less than 45 years of age. According to one of the largest studies involving 460,000 females, it was observed that the annual incidence rate of CT was 1.2 to 14.2 cases per 100,000.

Over the period of decades, several multicenter studies have observed different rates of incidence of benign cystic teratomas such as Marchetti observed a 20% occurrence of all ovarian tumors, while a large study by Blackwell et al. reported the occurrence to be 5%. Due to the rarity of this tumor, literature is skewed by either isolated case reports or small multicenter groups of cases. Thus leading to a broader range of incidence.

* Incidence:
  + Mature teratomas occur at an incidence of approximately 1.2 to 14.2 cases per 100,000 individuals worldwide.
  + Sacrococcygeal teratoma (SCT), the most common teratoma in newborns, occurs in about 1 per 20,000 to 40,000 live births.
  + Ovarian teratomas are common ovarian germ cell tumors and represent 10-20% of all ovarian neoplasms, with an estimated 8.9 cases per 100,000 women annually.
  + Mediastinal malignant teratomas are very rare, with an incidence of about 0.004 per 100,000 persons in the US.
* Age:
  + Immature teratomas are mostly seen in *younger patients and postpubertal males*.
  + Mature teratomas can occur at any age but commonly affect adolescents and young adults.
* Sex:
  + Sacrococcygeal teratomas are much more common in females, with a female-to-male ratio of approximately 3-4:1.
  + Excluding testicular teratomas, about 75-80% of teratomas occur in females.
  + Mediastinal teratomas show no consistent sex predilection.
* Geographical distribution:
  + Teratomas occur worldwide with no strong racial predilection reported.
  + Incidence rates and tumor types may vary slightly by region but overall are considered rare tumors globally.

## **Common Questions**

### **Can you have a teratoma on your face?**

Facial teratomas are possible, but rare. Head and neck teratoma tumors make up less than 6% of all teratomas.

### **Why do teratomas have teeth and hair?**

Teratomas often contain teeth, hair and other tissues because they form in your germ cells. Germ cells can turn into any type of tissue.

### **Can a teratoma have a heartbeat?**

It’s rare, but some teratomas can produce a “heartbeat” of sorts. Teratomas that develop into cardiac tissue can sometimes show heartbeat-like pumping activity.

### **What if my provider finds a teratoma on the fetus during pregnancy?**

If your provider finds a teratoma during the fetal stage of development, they’ll monitor your pregnancy closely. Small teratomas usually aren’t threatening and shouldn’t disrupt delivery. Large teratomas may require early delivery via C-section. Rarely, you may need fetal surgery to remove the teratoma before it leads to serious complications.

Before planning your treatment, your healthcare provider will take your unique situation into account. Treatment will depend on several factors, including your age, medical history, overall health and personal preferences.

**Doctor-patient conversation about teratoma**

Doctor: "You have been diagnosed with a teratoma, which is a type of tumor that arises from germ cells. These tumors are unique because they can contain different types of tissues like hair, muscle, or even bone."

Patient: "Is it cancer? Should I be worried?"

Doctor: "Most teratomas are benign, meaning they are not cancerous. However, some types, called immature teratomas, can behave more aggressively and may require additional treatment. The good news is that with early diagnosis and proper management, the outlook is generally very good."

Patient: "What symptoms should I watch for? How do you treat it?"

Doctor: "Symptoms depend on where the teratoma is located and its size. You might notice a lump, pain, or swelling. Sometimes, teratomas are found incidentally during imaging for other reasons. Treatment usually involves surgical removal of the tumor. If the teratoma is malignant or has spread, we may recommend chemotherapy or radiation after surgery."

Patient: "Are there any risks or complications?"

Doctor: "There can be risks related to the tumor growing or rupturing, which might cause pain or other issues. Rarely, teratomas can be associated with neurological symptoms if they affect the brain or cause immune reactions. That’s why close follow-up is important after treatment."

Patient: "What about the long-term outlook? Will it come back?"

Doctor: "Most patients do very well after surgery, especially if the tumor is completely removed. Some types, like growing teratoma syndrome, require ongoing monitoring and sometimes additional surgery. We will schedule regular check-ups and imaging to watch for any recurrence."

Patient: "Is there anything I can do to prevent it?"

Doctor: "Currently, there is no known way to prevent teratomas. The best approach is early detection and treatment. If you notice any new lumps, pain, or unusual symptoms, please contact us promptly."

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**NEUROBLASTOMA**

**DEFINITION AND DESCRIPTION**

Neuroblastoma is a cancer that starts in cells called neuroblasts. Neuroblasts are immature nerve cells. They are found in several areas of the body.

Neuroblastoma most often starts in the neuroblasts in the adrenal glands. The adrenal glands are located on top of each kidney. The glands make hormones that control important functions in the body. Other parts of the body that have neuroblasts and can get neuroblastoma include the spine, belly, chest and neck.

Neuroblastoma usually affects children age 5 or younger. Symptoms vary, depending on where it occurs in the body.

Some forms of neuroblastoma may go away on their own. Other forms of neuroblastoma need treatment. Treatments include surgery, chemotherapy, radiation therapy and bone marrow transplant. Your child's healthcare team will select the neuroblastoma treatments that are best for your child

### **Stages of neuroblastoma**

Healthcare providers classify neuroblastoma in children based on how advanced the cancer is and how fast it’s growing. They also consider whether it has spread (metastasized) to other parts of the body.

Using this information, providers determine the cancer’s risk level. Then they choose the most appropriate treatments. The stage of neuroblastoma used to be determined by how much neuroblastoma was found in the body after surgery. Now, the International Neuroblastoma Risk Group Staging System (INRGSS) is used. The stage of neuroblastoma is determined by how much tumor spread is seen on initial imaging studies (such as CT scan or MRI, as discussed below), called “image-defined risk factors.” The INRG stages of neuroblastoma are:

* Stage L1: This is the stage with the lowest risk. L1 tumors are confined to one body compartment and have not spread. Also, the tumor does not involve vital structures of the body (no image-defined risk factors are present).
* Stage L2: In this stage, the tumor is confined to one body compartment, but cancer cells can spread to regional lymph nodes, for instance. Also, there is involvement of vital structures of the body, such as tumor wrapping around large blood vessels (i.e., at least one image-defined risk factor is present).
* Stage M: In this stage, the cancer cells have spread to more than one body compartment – called “distant metastatic disease.” This stage carries the highest risk.
* Stage MS: This is a “special” category of neuroblastoma, affecting children younger than 18 months of age. In this stage, the cancer cells have spread (or metastasized) to either the skin, liver or bone marrow only. Children with stage MS neuroblastoma generally have an excellent prognosis. Stage MS neuroblastoma is usually considered low-risk disease

**Causes**

It's not clear what causes neuroblastoma. This cancer starts in immature nerve cells called neuroblasts. Neuroblasts are found in several areas of the body.

Neuroblastoma starts when neuroblasts 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 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**

The risk of neuroblastoma is higher in children. This cancer happens mostly in children age 5 and younger.

Children with a family history of neuroblastoma may be more likely to develop the disease. Yet, healthcare professionals think only a small number of neuroblastomas are inherited.

There are no known ways to prevent neuroblastoma.

**Symptoms**

Signs and symptoms of neuroblastoma may vary depending on what part of the body is affected. This cancer starts in immature nerve cells called neuroblasts. Neuroblasts are found in several areas of the body.

**Neuroblastoma in the belly** may cause symptoms such as:

* Belly pain.
* A lump under the skin that typically isn't tender when touched.
* Diarrhea or constipation.

**Neuroblastoma in the chest** may cause symptoms such as:

* Wheezing.
* Difficulty breathing.
* Changes to the eyes, including drooping eyelids and pupils that are different sizes.

Other symptoms that may indicate neuroblastoma include:

* Lumps of tissue under the skin.
* Eyeballs that seem to stick out from the sockets.
* Dark circles around the eyes that look like bruises.
* Back pain.
* Fever.
* Losing weight without trying.
* Bone pain.

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

Contact your child's healthcare professional if your child has any symptoms that worry you. Mention any changes in your child's behavior, habits or appearance.

## **Diagnosis**

A neuroblastoma diagnosis might start with a physical exam. Other tests and procedures include imaging tests and removing some tissue for testing. Your child's healthcare team may use a variety of tests and procedures to diagnose this cancer.

### **Physical exam**

A healthcare professional may examine your child to check for signs of neuroblastoma. The healthcare professional may ask you questions about your child's symptoms and health history.

### **Urine and blood tests**

A healthcare professional might test your child's urine and blood. The results can help the healthcare professional better understand your child's condition. Urine tests might look for high levels of chemicals made by neuroblastoma cells. For example, neuroblastoma can produce chemicals called catecholamines. These might be detected by a urine test.

### **Imaging tests**

Imaging tests make pictures of the body. They may help your child's healthcare team find the location of neuroblastoma and look for signs that it may have spread.

Imaging tests for neuroblastoma may include:

* X-ray.
* Ultrasound.
* Computerized tomography scan, also called CT scan.
* Magnetic resonance imaging, also called MRI.
* Metaiodobenzylguanidine scan, also called MIBG scan.

Not everyone needs each test. The healthcare team will decide which tests are needed based on your child's condition.

### **Biopsy**

A biopsy is a procedure to remove a sample of tissue for testing in a lab. To get the sample, a healthcare professional might put a hollow needle through the skin and into the cancer. The health professional uses the needle to draw out some cells for testing. Sometimes a surgeon removes the tissue sample during surgery.

In the lab, tests can check the tissue for signs of cancer. Other tests might look for changes in the DNA inside the cancer cells. Results from these tests may help your child's healthcare team make a treatment plan.

### **Bone marrow aspiration and biopsy**

Bone marrow aspiration and biopsy are procedures that involve collecting cells from the bone marrow. The cells are sent for testing. These procedures are used to check if neuroblastoma has spread to the bone marrow.

Bone marrow is the soft matter inside bones where blood cells are made. Bone marrow has a solid part and a liquid part. In a bone marrow aspiration, a needle is used to draw a sample of the fluid. In a bone marrow biopsy, a needle is used to collect a small amount of the solid tissue. The samples are typically taken from the hip bone.

**Treatment**

Treatments for neuroblastoma include surgery, radiation therapy, and medicines, such as chemotherapy and others. Healthcare teams consider many things when creating a treatment plan. These include the child's age, the stage of the cancer, the kinds of cells involved in the cancer and the DNA changes inside the cancer cells.

The healthcare team uses this information to say whether the neuroblastoma is low risk, intermediate risk or high risk. Neuroblastoma that is low risk or intermediate risk has a good chance for cure. High risk neuroblastoma can be more difficult to cure, so stronger treatments might be needed. What treatment or combination of treatments your child receives for neuroblastoma depends on the risk category.

### **Surgery**

During surgery for neuroblastoma, surgeons use cutting tools to remove the cancer cells. In children with low-risk neuroblastoma, surgery to remove the cancer may be the only treatment needed.

Whether the cancer can be removed completely depends on its location and size. Cancers that are attached to nearby vital organs may be too risky to remove.

In intermediate-risk and high-risk neuroblastoma, surgeons may try to remove as much of the cancer as possible. Other treatments, such as chemotherapy and radiation therapy, may then be used to kill remaining cancer cells.

### **Chemotherapy**

Chemotherapy treats cancer with strong medicines. Many chemotherapy medicines exist. Most chemotherapy medicines are given through a vein. Some come in pill form.

Children with intermediate-risk neuroblastoma often receive a combination of chemotherapy medicines before surgery. This improves the chances that the entire cancer can be removed.

Children with high-risk neuroblastoma often receive high doses of chemotherapy medicines to shrink the cancer. Chemotherapy also helps kill any cancer cells that have spread to other parts in the body. Chemotherapy often is used before surgery and before bone marrow transplant.

### **Radiation therapy**

Radiation therapy treats cancer with powerful energy beams. The energy can come from X-rays, protons or other sources.

Children with high-risk neuroblastoma may receive radiation therapy after chemotherapy and surgery. The radiation can help lower the risk that the cancer will come back.

### **Bone marrow transplant**

A bone marrow transplant, also called a bone marrow stem cell transplant, involves putting healthy bone marrow stem cells into the body. These cells replace cells hurt by chemotherapy and other treatments.

A bone marrow transplant might be an option for children with high-risk neuroblastoma. A bone marrow transplant for neuroblastoma uses the child's own blood stem cells. This kind of transplant is called an autologous stem cell transplant.

Before the transplant, a procedure is done to filter and collect blood stem cells from the child's blood. The stem cells are stored for later use. Next, the child receives high doses of chemotherapy to kill any remaining cancer cells. Then the blood stem cells are put back into the child's body. The transplanted cells can form new, healthy blood cells.

### **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 sometimes used with chemotherapy for high-risk neuroblastoma.

**Complications**

Complications of neuroblastoma may include:

* **Spread of the cancer.** With time, the cancer cells may spread to other parts of the body. Neuroblastoma cells most often spread to the lymph nodes, bone marrow, liver, skin and bones. When cancer spreads, it's called metastatic cancer.
* **Pressure on the spinal cord.** A neuroblastoma may grow and press on the spinal cord, causing spinal cord compression. Spinal cord compression may cause pain and paralysis.
* **Symptoms caused by cancer secretions.** Neuroblastoma cells may secrete chemicals that irritate other tissues. The irritated tissues can cause symptoms called paraneoplastic syndromes. Symptoms of paraneoplastic syndromes may include rapid eye movements and difficulty with coordination. Other symptoms include abdominal swelling and diarrhea.

## **Outlook / Prognosis**

The outlook for children with neuroblastoma varies. Cancer specialists measure cancer outlook by the five-year survival rate. Younger children with low- or intermediate-risk neuroblastoma have a good prognosis and a 90% to 95% survival rate. Older kids and those with high-risk neuroblastoma live cancer-free around 60% of the time. Healthcare providers and researchers continue to search for better treatments for this group of patients, and there are promising treatments on the horizon.

The prognosis depends on several factors, including:

* How old the child was at the time of diagnosis.
* The biological makeup of the tumor.
* If the tumor has spread to lymph nodes or other parts of the body.

## **Prevention**

It isn’t possible to prevent neuroblastoma. If you or your partner had neuroblastoma as a child or have a family history of the disease, talk to your provider. All children diagnosed with neuroblastoma should receive genetic counseling to see if genetic testing is needed. Genetic testing can tell you if your child has the gene markers for familial (inherited) neuroblastoma. However, it is important to remember that the inherited form of neuroblastoma is very rare – only 1% to 2% of cases. Additionally, some gene mutations that increase the risk of getting neuroblastoma are passed down through families – for instance, patients with Li Fraumeni syndrome (or a mutation in the p53 gene, which forms a tumor suppressor protein) are at increased risk for many types of cancers, including neuroblastoma.

## **Diagnostic Considerations**

A wide variety of neoplastic and nonneoplastic lesions might be confused with neuroblastoma. Wilms tumor and lymphoma are 2 malignant lesions that might be mistaken for neuroblastoma. The nonneoplastic lesions are particularly confusing, especially in the 5-11% of neuroblastomas that do not produce catecholamine metabolic by-products. Nonmalignant lesions that might be confused with neuroblastoma include ganglioneuroma and congenital mesoblastic nephroma.

**DIFFERENTIAL DIAGNOSIS**

* Dermoid cyst
* Ewing's sarcoma
* Germ cell tumour
* Hepatoblastoma
* Infantile fibromatosis
* Infection
* Lymphoma
* Rhabdomyosarcoma
* Small round cell sarcoma
* Wilms syndrome

## **Epidemiology**

### Frequency

Neuroblastoma is the most common cancer in infants. Approximately 700-800 cases are diagnosed each year in the United States, accounting for about 6% of cancers in children.Clinical frequency is approximately one case per 8000-10,000 children.

Neuroblastoma is more common in whites and is slightly more prevalent in boys than in girls (male-to-female ratio of 1.3:1). In rare cases, neuroblastoma is detected by prenatal ultrasound. About 37% of cases are diagnosed in infancy, and nearly 90% of cases are diagnosed before the age of 5 years. Median age at diagnosis is 19 months.Neuroblastoma is rare in people over the age of 10 years.Neuroblastoma is thought to occur sporadically, with 1-2% of cases considered familial.

## **Genomic features of neuroblastoma:**

* Somatic mutations:
  + Overall low mutation burden (~0.6 mutations per megabase).
  + Recurrently mutated genes include:
    - *ALK* (9.2% of cases), a tyrosine kinase receptor gene with activating mutations (common hotspots: F1174, F1245, R1275).
    - *PTPN11*, *ATRX* (loss-of-function mutations and deletions, especially in adolescents and young adults), *MYCN* (amplification and rare mutations), and *NRAS*.
  + Other mutations found in chromatin remodeling genes like *ARID1A* and *ARID1B* (~11% cases).
  + Rare germline variants enriched in *ALK*, *CHEK2*, *PINK1*, and *BARD1*.
* Copy number alterations and structural variants:
  + *MYCN* amplification is a hallmark of high-risk neuroblastoma and a strong adverse prognostic factor.
  + Hemizygous deletions of chromosome arms 1p and 11q are common and associated with poor prognosis.
  + Gains of 17q and chromothripsis (massive chromosomal rearrangements) are frequent in advanced disease.
  + Telomerase activation through *TERT* rearrangements and *CCND1* gains are implicated in tumor progression and relapse.
* Germline mutations and susceptibility loci:
  + Familial neuroblastomas are mostly caused by highly penetrant mutations in *ALK* and *PHOX2B*.
  + Genome-wide association studies (GWAS) have identified susceptibility loci including *BARD1*, *LMO1*, *CASC15/14*, *LIN28B*, and *HACE1*, which influence risk and clinical phenotype.
  + Germline copy number variations (e.g., in *NBPF23* at 1q21.1) also contribute to susceptibility.
* Relapse and progression:
  + Relapsed neuroblastomas show additional mutations in genes involved in MAPK signaling (e.g., *KRAS*, *FGFR1*), cell cycle regulation (*CCND1*, *CDK4*), and DNA repair (*BRCA1*, *CHEK2*, *WRN*).
  + Clonal evolution with subclonal mutations can occur during relapse.

**STAGING**

Stage 1: The cancer is still in the area where it started. It is on one side of the body (right or left). All visible tumours has been removed completely by surgery (although looking at the tumor’s edges under the microscope after surgery may show some cancer cells). Lymph nodes near the tumor are free of cancer (although nodes enclosed within the tumor may contain neuroblastoma cells).

Stage 2A: The cancer is still in the area where it started and on one side of the body, but not all of the visible tumor could be removed by surgery. Lymph nodes near the tumor are free of cancer (although nodes enclosed within the tumor may contain neuroblastoma cells).

Stage 2B: The cancer is on one side of the body, and it may or may not have been removed completely by surgery. Nearby lymph nodes outside the tumor contain neuroblastoma cells, but the cancer has not spread to lymph nodes on the other side of the body or elsewhere.

Stage 3: The cancer has not spread to distant parts of the body, but one of the following is true:

* The cancer can't be removed completely by surgery, and it has crossed the midline (defined as the spine) to the other side of the body. It may or may not have spread to nearby lymph nodes.
* The cancer is still in the area where it started and is on one side of the body. It has spread to lymph nodes that are relatively nearby but on the other side of the body.
* The cancer is in the middle of the body and is growing toward both sides (either directly or by spreading to nearby lymph nodes).

Stage 4: The cancer has spread to distant parts of the body such as distant lymph nodes, bones, liver, skin, bone marrow, or other organs (but the child does not meet the criteria for stage 4S).

Stage 4S (also called “special” neuroblastoma): The child is younger than 1 year old. The cancer is on one side of the body. It might have spread to lymph nodes on the same side of the body but not to nodes on the other side. The neuroblastoma has spread to the liver, skin, and/or the bone marrow. However, no more than 10% of marrow cells are cancer cells, and imaging tests such as an MIBG scan do not show cancer in the bone marrow.

Recurrent: While not a formal part of the staging system, this term is used to describe cancer that has come back (recurred) after it has been treated. The cancer might come back in the area where it first started or in another part of the body.

## 

**Treatment procedure and timeline for neuroblastoma**

## 1. Induction Phase (Duration: ~4-6 months)

* Goal: Achieve remission by shrinking or eliminating visible tumors.
* Treatment:
  + Intensive multi-agent chemotherapy cycles (typically 5 to 8 cycles). Common drugs include cisplatin, etoposide, vincristine, cyclophosphamide, doxorubicin, and topotecan.
  + Stem cell collection (autologous) occurs during this phase to harvest the patient’s own stem cells for later transplantation.
  + Surgery to remove residual tumor is usually performed after chemotherapy cycles, once the tumor size is reduced.
  + Emerging treatments like targeted ALK inhibitors or MIBG radiotherapy may be incorporated depending on tumor genetics and uptake.
* Typical cycle length: Each chemotherapy cycle lasts about 3-4 weeks, including treatment and recovery periods.

## 2. Consolidation Phase (Duration: ~1-2 months)

* Goal: Eradicate remaining cancer cells and consolidate remission.
* Treatment:
  + High-dose chemotherapy followed by one or two autologous stem cell transplants to rescue the bone marrow.
  + Radiation therapy to the primary tumor site and any residual disease detected by imaging (e.g., MIBG scans).
  + This phase may include tandem (back-to-back) stem cell transplants in some protocols.

## 3. Maintenance (Postconsolidation) Phase (Duration: ~6 months or longer)

* Goal: Reduce relapse risk and maintain remission.
* Treatment:
  + Retinoid therapy with 13-cis-retinoic acid (isotretinoin) to promote tumor cell differentiation.
  + Immunotherapy with anti-GD2 monoclonal antibodies (e.g., dinutuximab) combined with immune-stimulating cytokines like GM-CSF and IL-2.
  + Additional agents like eflornithine may be used for up to 2 years in some protocols.

## **QUESTION AND ANSWER SET**

## What is the stage (extent) of the neuroblastoma? What does this mean?

Neuroblastoma staging describes how far the cancer has spread in the body. Two main systems are used:

* International Neuroblastoma Risk Group Staging System (INRGSS) – based on imaging before any surgery:
  + L1: Localized tumor confined to one body compartment without involvement of vital structures (no image-defined risk factors, IDRFs).
  + L2: Locoregional tumor with one or more IDRFs, meaning it involves or is close to vital structures, making surgery more complex.
  + M: Distant metastatic disease (spread to distant lymph nodes, bone, bone marrow, liver, or other organs).
  + MS: Metastatic disease in children younger than 18 months with metastases limited to skin, liver, and/or bone marrow (less than 10% marrow involvement).
* International Neuroblastoma Staging System (INSS) – based on surgical findings:
  + Stages 1 to 4, with increasing spread and difficulty of surgical removal.
  + Stage 4S is a special category for infants with limited metastases and generally better prognosis.

What this means: The stage helps determine how advanced the cancer is, how difficult it may be to remove, and guides treatment planning and prognosis.

## 2. Which risk group does my child’s cancer fall into? What does this mean?

Risk groups (low, intermediate, high) are assigned based on:

* Stage of disease
* Age at diagnosis
* Tumor biology (e.g., MYCN gene amplification, DNA ploidy, histology)
* Other prognostic markers

Meaning:

* Low-risk: Usually localized disease with favorable biology; often treated with surgery alone or minimal chemotherapy.
* Intermediate-risk: May require chemotherapy and surgery; prognosis generally good.
* High-risk: Advanced stage, unfavorable biology (e.g., MYCN amplification); requires intensive multimodal therapy with less favorable prognosis.

## 3. **What else can you tell about cancer based on the tests that have been done?**

Tests like imaging (MRI, CT, MIBG scan), biopsy, bone marrow aspirates, and genetic studies provide information on:

* Tumor size, location, and spread
* Presence of metastases
* Tumor biology (MYCN amplification, ALK mutations)
* Bone marrow involvement
* Tumor markers in blood and urine (e.g., catecholamine metabolites)

This information refines staging and risk grouping and helps tailor treatment.

## 4**. Do we need to have any other tests before we discuss treatment options?**

Possible additional tests may include:

* MIBG scan or PET scan for detailed metastatic evaluation
* Bone marrow biopsy if not already done
* Genetic testing for tumor markers (MYCN, ALK)
* Cardiac and kidney function tests before chemotherapy
* Consultation with specialists for multidisciplinary planning

## 5. **How much experience do you have treating this type of cancer?**

You should ask your doctor about:

* Their personal experience and number of neuroblastoma cases treated
* The experience of the cancer center in pediatric oncology and neuroblastoma specifically
* Access to multidisciplinary teams and clinical trials

## 6. **Do we need to see any other types of doctors?**

Yes, the treatment team often includes:

* Pediatric oncologist (leads cancer treatment)
* Pediatric surgeon (for tumor removal)
* Radiation oncologist (if radiation is needed)
* Radiologist and pathologist (for diagnosis and monitoring)
* Supportive care specialists (nutrition, pain management, social work)
* Psychologists or counselors for emotional support

## 7. **Who else will be on the treatment team, and what do they do?**

* Nurses: Day-to-day care and education
* Pharmacists: Medication management
* Physical and occupational therapists: Help with recovery and development
* Social workers: Assist with family support and resources
* Child life specialists: Help children cope with treatment

## 8. When deciding on a treatment plan

* **Does neuroblastoma need to be treated? Why or why not?**  
  Most neuroblastomas require treatment due to their potential to grow and spread. Some low-risk tumors may be observed if small and asymptomatic.
* What are our treatment options?  
  Surgery, chemotherapy, radiation therapy, immunotherapy, stem cell transplant, targeted therapy, or combinations thereof.
* Does one type of treatment increase the chance of cure more than another?  
  High-risk neuroblastoma requires multimodal treatment for the best chance of cure. Low-risk may be cured with surgery alone.
* Are there any clinical trials we should consider?  
  Ask about ongoing trials that may offer new therapies.
* Which treatment do you recommend? Why?  
  Your doctor will tailor recommendations based on risk group, tumor biology, and overall health.
* Should we get a second opinion? How do we do that? Can you recommend a doctor or cancer center?  
  Second opinions are common and encouraged. Your doctor or hospital can refer you to specialized pediatric cancer centers.
* How soon do we need to start treatment?  
  Usually as soon as possible after diagnosis and staging.
* What should we do to be ready for treatment?  
  Prepare for hospital visits, discuss logistics, and address emotional support.
* How long will treatment last? What will it be like? Where will it be done?  
  Treatment length varies (months to over a year), involving hospital stays and outpatient visits, at specialized pediatric oncology centers.
* How will treatment affect our daily lives?  
  There will be disruptions due to hospital visits, side effects, and recovery time.
* How long will it take my child to recover from treatment?  
  Recovery varies; some effects are immediate, others take months to years.
* What are the possible side effects from treatment? What can be done for them?  
  Side effects include nausea, infection risk, fatigue, hearing loss, growth delays; supportive care helps manage these.
* Which side effects start shortly after treatment and which ones might develop later on?  
  Acute side effects occur during/soon after treatment; late effects can include organ dysfunction, secondary cancers.
* How might treatment affect my child’s ability to learn, grow, and develop?  
  Some therapies can affect development; early intervention and monitoring are important.
* Will treatment affect my child’s ability to have children someday? Can we do anything about this?  
  Some treatments may impact fertility; fertility preservation options should be discussed before treatment.
* Will my child have a higher long-term risk of other cancers?  
  Yes, some treatments increase secondary cancer risk; long-term follow-up is essential.

## 9. During and after treatment

* How will we know if the treatment is working?  
  Through imaging, tumor markers, and clinical assessment.
* Is there anything we can do to help manage side effects?  
  Yes, medications, nutrition, and supportive therapies.
* What symptoms or side effects should we tell you about right away?  
  Fever, severe pain, bleeding, difficulty breathing, or other urgent symptoms.
* How can we reach you or someone on your team on nights, weekends, or holidays?  
  Your care team should provide emergency contact information.
* Who can we talk to if we have questions about costs, insurance coverage, or social support?  
  Social workers or financial counselors at the treatment center.
* What are the chances that the cancer will come back after treatment? What would we do if this happens?  
  Depends on risk group; relapses require additional treatment and clinical trials may be options.
* What type of follow-up will my child need after treatment?  
  Regular visits with imaging and labs for years to monitor for recurrence and late effects.
* Do you know of any local or online support groups where we can talk to other families who are coping with neuroblastoma or childhood cancer?  
  Many hospitals and cancer organizations offer support groups and online forums.

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### **Retinoblastoma**

Retinoblastoma is a type of eye cancer that starts in your retina, the light-sensing layer of cells at the back of your eye. It’s the most common childhood eye cancer.

Retinoblastoma can happen in one or both eyes. About 1 in 4 cases affect both eyes. Experts suspect it happens because of a malfunction in young, developing retinal cells. Diagnosis occurs before age 3 in 4 out of 5 cases. In rare cases, adults can also develop the condition after a pause in the tumor’s early development.

#### **Types of retinoblastoma**

There are three types of retinoblastoma:

* Unilateral: This means “one-sided,” so it affects one eye only.
* Bilateral: This means “two-sided,” so it affects both eyes.
* Trilateral: This means you have cancer in three places. Each eye reflects one of those places. The third place is in the pineal gland inside your brain. (Cancer affecting that gland is called pineoblastoma.)

About 60% of retinoblastoma cases are one-sided. Bilateral and trilateral cases make up the other 40%.

Retinoblastoma is rare. There are about 3.3 cases per 1 million people under age 20. In that age group, there are a little over 300 new cases annually in the U.S. and slightly under 9,000 new cases worldwide.

## **Symptoms and Causes**

Because the condition is typically diagnosed before age 3, children often can’t describe their symptoms or what they’re experiencing. Instead, the symptoms are visible changes in eye appearance or differences in how your child behaves.

#### **Leukocoria**

The earliest and most common symptom of retinoblastoma is the pupil of your eye appearing white (leukocoria) or pale-colored in certain settings, especially seen in photos taken in dim places that also use a flash for illumination. It can happen in one or both eyes.

#### **Other symptoms of retinoblastoma**

While retinoblastoma commonly happens in children before they can talk, there are also other signs and symptoms that can signal its development, including:

* Eyes that have trouble following movement or don’t follow it at all.
* Misaligned eyes (strabismus).
* Pain (it may cause your child to cry more or be fussier than usual, or they might have trouble sleeping or feeding).
* Enlarged eye (buphthalmos).
* Bulging eye (proptosis).
* Blood in the front chamber of your eye (hyphema).
* Infection, swelling or inflammation of your eye or surrounding tissue (orbital cellulitis).

### **What causes retinoblastoma?**

Retinoblastoma is a type of cancer where retinal cells malfunction and start to multiply uncontrollably. As they do, they can form tumors and damage surrounding tissues. If they keep growing unchecked, eventually, those malfunctioning cells spread (metastasize) beyond the original tumor, and cancer appears in other places in your body.

The malfunction that causes healthy cells to turn into retinoblastoma starts in your DNA.

Your cells use DNA like a cookbook. You inherit DNA from both of your biological parents, so it’s like they each give you part of their cookbook, so you can make a full cookbook of your own.

But sometimes, you can have an error in your DNA. Your cells only know how to follow the recipes in the book exactly, so a DNA error means your cells only know how to make the recipe incorrectly. That can cause those cells to grow and multiply uncontrollably.

Experts recommend genetic testing and counseling for children with retinoblastoma regardless of whether or not it was inherited. They also recommend testing for biological siblings and other family members.

The mutation that causes retinoblastoma affects *RB1*, a tumor suppressor gene. Tumor suppressor genes are responsible for normal development of the tissues (retina). They act like brakes and control cell reproduction and growth processes. A mutation in *RB1* means your retinal cells can grow uncontrolled into a tumor. Retinoblastoma can also happen with “deletion” of chromosome 13p, which is the location of the *RB1* gene.

In rare instances, people can have a benign retinal growth called a retinoma. These are like precursors to retinoblastoma, but they stop growing for some reason. Later in life, a retinoma may start growing again and turn into retinoblastoma.

There are two main ways that DNA errors that cause retinoblastoma can happen:

* Sporadic: This is when an error happens while your cells copy a parent’s DNA. It’s like accidentally introducing a typo while hand-copying a recipe. The recipe you copied from was sound, but the new error means your recipe is now incorrect. Sporadic cases of retinoblastoma affect one eye only.
* Inherited: This is when one or both biological parents have DNA with the error. Your cells copy their DNA correctly, but that also includes the pre-existing typo. Retinoblastoma has autosomal dominant inheritance. That means you have roughly a 50% chance of inheriting the gene if one parent has it and a 75% chance if both parents have it. But biological parents may not have retinoblastoma even if their child has the inherited form. That’s because some people are carriers, meaning they have the mutation without it causing them to have the condition.

Inheriting a gene mutation also determines what form of retinoblastoma your child has. Inherited cases are usually bilateral and less often unilateral.

A sibling of a child with retinoblastoma also has an increased chance of developing it. When both parents are unaffected by retinoblastoma, biological siblings of the affected child have a 4% to 7% risk of having retinoblastoma, too.

### **Complications of retinoblastoma**

Retinoblastoma can damage surrounding tissues. It can cause partial or total blindness in the affected eye(s).

Because it’s a type of cancer, there’s also a risk of retinoblastoma spreading (metastasizing) to other parts of your body. Once it does, it becomes even more dangerous, so preventing that spread is a key part of treatment. One dangerous way it can spread is through the optic nerve to your brain, where it becomes a new brain cancer tumor.

The genetic mutations that can cause retinoblastoma also increase your risk of developing other types of cancer. There’s a 1% cumulative risk per year of developing another cancer (for example, about 20% at 20 years).

The most likely cancers are:

* Sarcomas: These affect bones and connective tissues.
* Melanomas: These affect your skin, eyes and mucus membranes, like those inside of your mouth and nose.
* Lung cancers: Because of the intricate blood vessel connections in the lungs, cancers here can easily spread anywhere else in your body.

## **Diagnosis and Tests**

Parents (or caregivers) may be the first to see leukocoria and tell their child’s pediatrician, who can then also look for it. A pediatrician (or another healthcare provider with a similar role) can confirm leukocoria during an exam, or they might see leukocoria during routine physical exams that monitor child development.

Once a pediatrician sees leukocoria, the next step is usually an urgent referral to an ophthalmologist or other eye care specialist. An eye specialist will try to see retinoblastoma directly by looking at the eye’s interior. For young children, that may involve using medicated drops to dilate their pupils or doing an eye exam under anesthesia.

Imaging scans are likely, as these can look for harder-to-see tumors in the other eye or corresponding tumors in the brain (like pineoblastoma).

Imaging scans they might use include:

* Ultrasound: This scan can show calcium accumulations that are common with retinoblastoma.
* Computed tomography (CT) scan: Retinoblastoma often involves calcium accumulations, which are also visible on CT scans.
* Magnetic resonance imaging (MRI) scan: This is the best scan for detailed images of the different tissues and structures inside your body. It takes longer and is costlier, so it’s often not the first test. Still, it’s a vital way to see just how far a tumor has spread or detect tumors elsewhere in the other eye or brain.
* Positron emission tomography (PET) scan: This test may happen early in the diagnosis and treatment process or long after. It’s especially useful for detecting if the tumor has metastasized to other places or if other tumors have developed elsewhere.

## **Management and Treatment**

There are multiple ways to treat retinoblastoma. Often, treatment involves a combination of methods. They can happen simultaneously or in sequence. The treatment methods include (but aren’t limited to):

* Chemotherapy: This approach uses drugs that attack cancerous cells’ weaknesses directly. That can help avoid surgery that might involve a loss of vision. It can also cause tumors to shrink enough that other treatments can destroy the remaining cancerous cells. It can be local, meaning it happens via targeted injections or infusions through the artery (intraarterial). It can also be systemic, meaning it happens via a standard intravenous (IV) infusion. The method of administration varies depending on your specific case and needs.
* Radiation therapy: This involves using high-frequency energy to destroy tumor cells. That can happen from outside your body with treatments like external beam radiation therapy (EBRT) or inside your body with methods like brachytherapy. However, treatment usually avoids this because of long-term complication risks.
* Focal therapies (cryotherapy, thermotherapy, laser therapy, etc.): Focal treatments get their name because they “focus” on destroying tumor cells directly. That can involve thermotherapy or laser therapy, which use intense heat energy to destroy the cells, or cryotherapy, which uses intense cold to destroy the cells instead of heat.
* Surgery: Surgery is most likely when there’s a risk of retinoblastoma spreading. This usually involves a surgery like enucleation, which means removing your eye. This prevents the cancer from spreading further. By the time this surgery is necessary, the cancer likely has already damaged your affected eye enough to cause vision loss.
* Other therapies and treatments: These can vary widely and usually help with the side effects of other treatments. One example of treatments like this would be medications that can help with nausea and vomiting, which are common with chemotherapy. Because there are so many support treatments like this, your provider is the best person to tell you what they recommend for your specific case and needs.

## **Outlook / Prognosis**

The outlook for retinoblastoma depends strongly on how long it takes to diagnose and treat it, but the odds, in general, are very good. The overall survival rate for pediatric retinoblastoma is 95%. The odds of a good outcome — including avoiding loss of vision — are best with a diagnosis before age 2.

People who survive retinoblastoma will need lifelong surveillance for new cancers. This usually involves yearly scans or other tests that can detect new tumors. Your provider can tell you what surveillance measures they recommend for your case.

## **Prevention**

Retinoblastoma happens because of genetic mutations, so there’s no way to prevent it entirely. If you have a family history of retinoblastoma or know you carry a genetic mutation that causes it, genetic counseling can help you understand the risk of passing it on to a biological child.

### **When should I call my healthcare provider about retinoblastoma?**

Call your provider if you notice any signs of retinoblastoma or changes in your child’s eyes or vision. Talk to your provider if you or your partner has a family history of retinoblastoma or you know you have the RB1 gene mutation. You may want to consider genetic counseling before having children.

### **What do I need to know if I have a family history of retinoblastoma?**

If you have a family history of retinoblastoma, be sure to schedule regular eye exams for your child and other family members. The RB1 gene that causes retinoblastoma can also cause retinocytoma, a benign (noncancerous) eye tumor. Retinocytoma can develop in people of all ages.

**DIFFERENTIAL DIAGNOSIS**

* Congenital cataract
  + Presented with white pupils but no intraocular mass; diagnosed by slit-lamp exam.
* Coats’ disease
  + Idiopathic retinal telangiectasia with subretinal exudates causing yellowish-white reflex; usually unilateral and affects older children (6–8 years); lacks calcifications seen in retinoblastoma.
* Persistent fetal vasculature (PFV) / Persistent hyperplastic primary vitreous
  + Congenital anomaly with remnant embryonic vitreous tissue; presents with leukocoria but no retinal mass.
* Retinopathy of prematurity (ROP)
  + Occurs in premature infants; abnormal retinal vascular development with fibrosis and detachment.
* Toxocariasis
  + Parasitic infection causing retinal scarring and inflammation; may mimic leukocoria.
* Vitreous hemorrhage
  + Blood in vitreous can cause white reflex; history and imaging help differentiate.
* Astrocytic hamartoma
  + Benign retinal tumor that may resemble retinoblastoma on exam.
* Choroidal coloboma
  + Congenital defect causing white reflex in some cases.
* Exudative retinal detachment
  + Secondary to various causes, can mimic tumor.
* Orbital cellulitis or endophthalmitis (in cases of inflammation or redness)
  + May mimic advanced retinoblastoma with inflammation.

**EPIDEMIOLOGY**

**Incidence**

Retinoblastoma is the most common primary intraocular malignancy in children, representing approximately 3% of all pediatric tumors. This pathology is the 2nd most common intraocular malignant tumor overall. The incidence ranges from 1 in 14,000 to 1 in 20,000 live births, with approximately 300 new cases diagnosed annually in the U.S. While relatively rare, retinoblastoma’s potential for severe morbidity and mortality underscores the importance of understanding its epidemiological patterns.

The global incidence of retinoblastoma is estimated to be approximately 1 in 15,000 to 20,000 live births, resulting in around 8,000 new cases annually. This figure corresponds to about 10 to 15 cases per million children younger than 5. The incidence is relatively constant across populations, reflecting a stable mutation rate in the *RB1* gene, which drives most cases.

Retinoblastoma primarily affects children younger than 5, with a median age at diagnosis of 12 months for bilateral cases and 24 months for unilateral cases. Approximately 95% of cases are diagnosed before age 5, with 90% identified before age 3. Meanwhile, occurrence in older children and adults is exceedingly rare.

Incidence varies geographically, with reported rates of 6 cases per million in Mexico and 4 cases per million in the U.S. The highest incidence has been observed in India and Africa. Survival rates and outcomes vary significantly between high-income (HICs) and low- and middle-income countries (LMICs). In HICs, survival rates exceed 95% due to early diagnosis, advanced medical infrastructure, and access to comprehensive care. Most cases are detected at an early stage, allowing for eye-preserving treatments. In LMICs, survival rates range from 30% to 60%, with even lower rates in some regions of sub-Saharan Africa and South Asia. Late diagnosis and limited access to specialized care often result in worse outcomes, frequently requiring enucleation or leading to extraocular spread and metastatic disease.

Retinoblastoma affects male and female individuals equally, showing no significant sex predilection. The disease also lacks ethnic or racial predisposition, with incidence rates remaining similar across different populations.

**Hereditary vs. Sporadic Cases**

Retinoblastoma is broadly categorized into hereditary and sporadic forms, each with distinct epidemiological patterns. Hereditary retinoblastoma accounts for 45% of cases and often presents as bilateral or multifocal tumors. Affected individuals inherit a germline *RB1* mutation, which carries a 50% chance of transmission to offspring. These cases tend to be diagnosed earlier than sporadic cases, with a median age of onset of 12 months. In addition to eye involvement, hereditary retinoblastoma is associated with an increased risk of secondary malignancies later in life, including osteosarcoma, soft tissue sarcoma, and melanoma.

Sporadic retinoblastoma comprises 55% of cases and typically manifests as a unilateral, unifocal tumor. Unlike hereditary cases, sporadic retinoblastoma results from 2 somatic mutations in the *RB1* gene occurring within retinal cells. The median age of onset is later, around 24 months. Since these cases lack germline mutations, affected individuals do not have an elevated risk of developing secondary malignancies.

**Survival Rates**

Retinoblastoma is rarely fatal in HICs, with 5-year survival rates exceeding 95%. Early diagnosis and the use of eye-preserving treatments, such as IAC and focal therapies, contribute to these high survival rates. In contrast, survival rates in LMICs are significantly lower due to limiting factors, including late diagnosis, poor access to specialized care, and a high prevalence of advanced disease at the time of presentation. Many children in these regions present with extraocular retinoblastoma, a form of the disease that carries a poor prognosis and often results in fatality without aggressive treatment.

**Global Disparities**

Global disparities exist in the management of retinoblastoma. In LMICs, delayed diagnosis often results from restrictive cultural beliefs, limited access to healthcare, and a lack of awareness among caregivers and primary care providers, contributing to late-stage presentations that significantly increase mortality rates. Furthermore, many LMICs lack the necessary infrastructure and trained personnel to provide advanced diagnostic imaging, chemotherapy, and radiotherapy, which are essential for effective treatment. Economic barriers also play a major role, as the high costs of treatment, including systemic chemotherapy and specialized surgeries like enucleation, create significant challenges in resource-limited settings.

**Genetic and Familial Patterns**

Children with hereditary retinoblastoma have a 50% chance of passing the germline *RB1* mutation to their offspring. Siblings of affected individuals also have an increased risk of developing retinoblastoma. Advances in genetic testing have made it possible to identify at-risk infants, enabling regular surveillance and early tumor detection, which significantly improves outcomes.

**Epidemiological Trends**

Advances in early detection, imaging, and eye-preserving therapies have significantly improved survival rates in HICs, with a focus on minimizing treatment-related morbidity. The introduction of innovative treatments, such as IAC, IVC, and molecular targeted therapies, has revolutionized the management of retinoblastoma. Efforts to address global disparities in care are being made through organizations like the International Agency for the Prevention of Blindness (IAPB) and the Retinoblastoma World Alliance, which are improving awareness, training, and healthcare access in LMICs. Public health campaigns in LMICs aim to educate caregivers and healthcare providers about early signs, such as leukocoria, promoting earlier diagnosis.

The epidemiology of retinoblastoma reflects both the advancements in pediatric oncology and the persistent global disparities in healthcare access and outcomes. While survival rates in HICs are near 100%, children in low-resource settings face significant barriers to diagnosis and treatment, leading to high mortality rates. Efforts to bridge these gaps, including public health initiatives, improved genetic screening, and international collaborations, are essential to ensure that every child, regardless of geography or socioeconomic status, has access to life-saving care for retinoblastoma.

## **Common Chemotherapy Drugs Used in Retinoblastoma and Their Side Effects**

| **Drug** | **Mechanism/Use** | **Common Side Effects** |
| --- | --- | --- |
| Melphalan | Alkylating agent, used mainly in intra-arterial chemotherapy (IAC) | - Neutropenia (low white blood cells) in ~11-15% of cases  - Local ocular effects: eyelid edema, ptosis, conjunctival swelling, forehead hyperemia  - Rare vascular complications (ophthalmic artery spasm, retinal artery occlusion)  - Transient cytopenias, rarely requiring transfusion or hospitalization |
| Carboplatin | Platinum-based DNA crosslinker, systemic and periocular use | - Nephrotoxicity (kidney damage)  - Ototoxicity (hearing loss), especially in infants younger than 6 months  - Neuropathy  - Hypomagnesemia  - Local periocular redness and swelling when injected near the eye |
| Cisplatin | Platinum-based DNA crosslinker, systemic use | - Nephrotoxicity  - Ototoxicity (hearing loss)  - Nausea, vomiting |
| Vincristine | Microtubule inhibitor, systemic chemotherapy | - Peripheral neuropathy (tingling, numbness in hands and feet)  - Constipation  - Hair loss |
| Etoposide | Topoisomerase II inhibitor, systemic chemotherapy | - Allergic reactions  - Hepatotoxicity  - CNS toxicity  - Hypotension  - Alopecia  - Mucositis  - Risk of secondary acute myelogenous leukemia (rare, with high doses) |
| Cyclophosphamide | Alkylating agent, systemic chemotherapy | - Hemorrhagic cystitis (bladder irritation/bleeding)  - Bone marrow suppression  - Nausea, vomiting |
| Dactinomycin (Actinomycin D) | Antineoplastic antibiotic, systemic use | - Bone marrow depression  - Nausea  - Mucositis |
| Doxorubicin | Antineoplastic antibiotic, systemic use | - Cardiotoxicity (dose-dependent)  - Mucositis  - Alopecia  - Red urine discoloration |

## Intra-Arterial Chemotherapy (IAC) Specifics and Side Effects

* Delivered directly into the ophthalmic artery to concentrate drug in the eye, reducing systemic toxicity.
* Most common systemic side effects are neutropenia and transient cytopenias, usually mild and self-limited.
* Local ocular side effects include eyelid swelling, ptosis, conjunctival chemosis, forehead redness, and rare vascular events such as ophthalmic artery spasm or retinal artery occlusion.
* Serious complications like stroke or permanent vascular occlusion are very rare with proper technique.
* No reported cases of secondary cancers directly attributed to IAC; however, germline retinoblastoma patients remain at risk due to their genetic predisposition.

## Systemic Chemotherapy Side Effects

* More systemic side effects than IAC, including nausea, vomiting, hair loss, fatigue, increased infection risk (due to low white blood cells), easy bruising or bleeding, and mouth sores.
* Platinum agents (carboplatin, cisplatin) can cause hearing loss, especially in very young children.
* Vincristine can cause nerve damage leading to numbness or tingling.
* Cyclophosphamide may cause bladder irritation (hemorrhagic cystitis).
* Long-term risks include secondary malignancies (e.g., acute myelogenous leukemia), especially with high-dose chemotherapy.

## Supportive Care During Chemotherapy

* Anti-nausea medications to reduce vomiting.
* Blood counts monitored regularly; transfusions or antibiotics given as needed.
* Hearing tests during and after treatment to monitor ototoxicity.
* Hydration protocols to protect kidneys during platinum-based chemotherapy.

**Retinoblastoma genomic**

* Cause: Retinoblastoma arises due to biallelic inactivation of the RB1 tumor suppressor gene located on chromosome 13q14. Both copies of *RB1* must be mutated or lost for tumor development, following the classic "two-hit" hypothesis.
* Hereditary vs. non-hereditary:
  + *Hereditary retinoblastoma* involves a germline mutation in one *RB1* allele present in all body cells, inherited in an autosomal dominant pattern with ~90% penetrance. A second somatic mutation in retinal cells leads to tumor formation. These cases often present as bilateral or multifocal tumors and carry a risk of secondary cancers (including trilateral retinoblastoma with pineal tumors).
  + *Non-hereditary retinoblastoma* involves two somatic mutations in retinal cells only, usually resulting in unilateral tumors and no risk to offspring.
* Mutation spectrum:
  + Over 900 distinct mutations in *RB1* have been reported, including nonsense, frameshift, splice-site mutations, and large deletions or rearrangements.
  + Small genetic rearrangements are most common (~79%), with large rearrangements in ~9-21%.
  + Mutations causing premature stop codons (nonsense, frameshift) predominate.
  + Some splice-site mutations may cause incomplete penetrance.
  + Novel mutations continue to be identified.
* Detection and clinical relevance:
  + Genetic testing for *RB1* mutations is critical for diagnosis, family screening, and prenatal testing.
  + Approximately 40–45% of retinoblastomas have detectable *RB1* mutations, with germline mutations found in ~66–90% of bilateral cases.
  + Identification of *RB1* mutations guides surveillance for secondary tumors and informs genetic counseling.
* Other genetic factors:
  + Rare cases involve amplification of the *MYCN* oncogene without *RB1* mutation, associated with aggressive disease.
  + Loss of *RB1* also leads to genomic instability promoting tumor progression.

**DOCTOR PATIENT CONVERSATION**

Doctor: “Your child has been diagnosed with retinoblastoma, a tumor that starts in the retina, usually in children under 5 years old. I want to explain what this means, the treatment options available, and answer any questions you have.”

* Parent: “What exactly is retinoblastoma? Is it cancer?”
* Doctor: “Yes, it is a cancer of the eye’s retina. The good news is that with early diagnosis and treatment, many children can be cured, and we have several treatment options depending on the tumor’s size and spread.”
* Doctor: “We’ve done imaging and eye exams to determine the stage of the tumor — whether it’s inside one eye or both, and whether it has spread beyond the eye. This helps us decide the best treatment.”
* Parent: “What tests have been done so far? Do we need more?”
* Doctor: “We’ve done an MRI to look for any spread and an eye exam under anesthesia. Sometimes we need additional imaging or genetic testing to understand the full picture.”
* Doctor: “Treatment may include chemotherapy, laser therapy, cryotherapy, radiation, or surgery. If only one eye is affected and the tumor is large, surgery to remove the eye might be necessary. For smaller tumors or bilateral disease, we try to save the eyes and vision with chemotherapy and focal treatments.”
* Parent: “What are the side effects? How will treatment affect my child?”
* Doctor: “Side effects vary by treatment but can include fatigue, nausea, risk of infection, and effects on vision. We will support you through this with a multidisciplinary team.”
* Parent: “Are there clinical trials or newer treatments we should consider?”
* Doctor: “Yes, we can discuss clinical trials if appropriate. We always aim to use the best available treatments tailored to your child.”
* Doctor: “You will have a team including pediatric oncologists, ophthalmologists, nurses, social workers, and genetic counselors to support your child and family throughout treatment and follow-up.”
* Parent: “How soon do we need to start treatment? What happens after?”
* Doctor: “We usually start treatment as soon as possible. After treatment, your child will need regular check-ups to monitor for recurrence and manage any late effects.”
* Parent: “Can we get a second opinion?”
* Doctor: “Absolutely, and I can help refer you to specialized centers if you wish.”

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**Nephroblastoma (Wilms Tumor)**

Wilms tumor is a kidney tumor found almost always in children. This condition represents nearly 90% of kidney tumors in children. In some cases, Wilms tumor is part of a group of conditions that are present at birth. These are called congenital syndromes.

Wilms tumor is also called Wilms’ tumor or nephroblastoma. Usually, there is only one tumor on one kidney, but there can sometimes be tumors on both kidneys (bilateral) or more than one cancerous spot on one kidney

Although there’ve been rare cases in adults, Wilms tumor is a cancer found mostly in children under 15 years old. About 95% of cases of this disease are diagnosed by the time a child is 10 years old.

The risk is higher in Black children and lower in Asian children. Wilms tumor is a little bit more common in girls than boys.

Wilms tumor has been passed down in the genes of a very small percentage of families.

There are an estimated 500 new cases of Wilms tumor diagnosed in the U.S. every year.

### **What types of congenital (present at birth) syndromes are often found with Wilms tumor?**

Very rarely, people with Wilms tumor also have other congenital syndromes. Some of these syndromes include:

* Beckwith-Wiedemann syndrome: Children with this syndrome have a 5% to 10% risk of developing Wilms. This syndrome is classified as an overgrowth syndrome — body parts grow larger and one side of the body doesn’t always match the other side.
* WAGR syndrome: Children with this syndrome have about a 50% chance of developing Wilms tumor. (The “W” in the name stands for Wilms.) Other complications include lack of an iris in the eye (Aniridia) and Genital or Renal issues.
* Denys-Drash syndrome (also known as Drash syndrome): Children with this grouping of medical conditions have a 90% chance of developing Wilms. Other issues involve their genitals and kidneys.

## **Symptoms and Causes**

Signs and symptoms of Wilms tumor include:

* A swollen spot or hard lump in your child’s abdomen (stomach area). The lump or swelling can be painful, but it’s usually not.
* Pain in their abdomen.
* Blood in their urine (hematuria).
* Fever.
* High blood pressure (hypertension). This in turn may cause your child to have nosebleeds, headaches and blood in their eye.

### **What causes Wilms' tumor?**

Although a small number of people inherit a gene for Wilms tumor, we don’t really know what causes it.

## **Diagnosis and Tests**

If you’ve found a lump near your baby’s diaper line, or you’ve had to move to bigger diapers because of the lump, your healthcare provider may decide to test for Wilms tumor. The tumors sometimes get quite big, even bigger than the kidney itself.

If your child has one of the syndromes or genetic issues associated with Wilms, you and your provider may decide to do regular testing.

Tests to diagnose Wilms tumor include:

* A physical exam that includes pressing down carefully on your child's abdomen.
* Imaging tests like abdominal ultrasound, CT scan – usually with contrast. Your provider might order an X-ray or CT scan of your child's chest to find out if cancer has spread (metastasized) to their lungs. Imaging tests can show if your child has a tumor. Your provider can also use the tests to tell the difference between Wilms tumor and other types of kidney cancer.
* Laboratory tests of blood and urine, including liver function and blood clotting tests.
* A biopsy, which means that tissue from the tumor is removed and sent to the laboratory for testing.

### **Staging and Wilms tumor**

There are two different ways to stage Wilms tumor. Staging is the name for the way that healthcare providers determine if and how far the cancer has spread beyond its original location. The higher the number, the farther the cancer has spread.

Throughout Europe, healthcare providers use the International Society of Paediatric Oncology (SIOP) staging system. In the U.S. and Canada, healthcare providers use the Children’s Oncology Group (COG) staging system.

One difference between the two systems is that the COG system uses surgery to stage the tumor before chemotherapy. The SIOP system uses surgery after chemotherapy to do the staging.

Under the COG system, staging is as follows:

* A Stage I tumor is only in your child's kidney and is removed completely during surgery.
* A Stage II tumor has grown past your child's kidney, but is also removed completely.
* A Stage III tumor isn’t able to be removed completely and some tissue remains in your child's abdominal area.
* A Stage IV tumor has grown beyond your child's abdomen and pelvis to places like their lungs, liver, bone or brain.
* A Stage V tumor is bilateral, or present in both kidneys. Your provider will do staging on each kidney separately.

## **Management and Treatment**

Wilms tumor is almost always treated with a combination of surgery and chemotherapy. Sometimes, treatment will include radiation therapy.

Many children with low-risk tumors are treated with surgery alone if the tumor hasn’t spread and can be taken out completely. Sometimes, your child may be treated with chemotherapy before surgery to make the tumor smaller and surgery safer.

Most chemotherapy is given through a vein (intravenously or I.V.). It can happen on an outpatient basis or in a hospital.

Your child may have side effects from the chemotherapy or radiation. If so, be sure to tell your provider. There are things you can do or medicines your child can take to lessen side effects.

## **Diagnostic Considerations**

Conditions to be considered in the differential diagnosis of Wilms tumor include the following:

* Mesoblastic nephroma - Most common renal tumor in the first month of life
* Renal cell carcinoma
* Clear cell sarcoma of the kidney
* Rhabdoid tumor of the kidney
* Nonmalignant mass
* Hydronephrosis
* Multicystic kidney disease
* Renal cyst
* Renal thrombosis
* Dysplastic kidney
* Renal hemorrhage

## **Differential Diagnoses**

* Pediatric Neuroblastoma
* Pediatric Polycystic Kidney Disease
* Pediatric Rhabdomyosarcoma

## 

## **Epidemiology**

### United States data

Wilms tumor affects approximately 10 children and adolescents per 1 million before age 15 years. Therefore, it accounts for 6-7% of all childhood cancers in North America. As a result, about 450-500 new cases are diagnosed each year on this continent. In 5-10% of patients, both kidneys are affected at the same time (synchronous bilateral Wilms tumor) or one after the other (metachronous bilateral Wilms tumor).

### International data

Wilms tumor appears to be relatively more common in Africa and least common in East Asia.The incidence in Europe is similar to that reported in North America.

Low-income countries have a higher median incidence of Wilms tumor (9.8 age-standardized rate [ASR] per million) than high-income (8.6 ASR per million) and middle-income countries (6.1 ASR per million).

### Race-, sex-, and age-related demographics

Wilms tumor is relatively more common in Blacks than in Whites and is rare in East Asians. Estimates suggest 6-9 cases per million person years in Whites, 3-4 cases per million person years in East Asians, and more than 10 cases per million person years among Black populations.

Among patients with unilateral Wilms tumor enrolled in all NWTSG protocols, the male-to-female ratio was 0.92:1. For patients with bilateral disease, the male-to-female ratio was 0.60:1.

The median age at diagnosis of Wilms tumor is approximately 3.5 years. The median age is highest for patients with unilateral unicentric disease (36.1 mo) and lowest for those with synchronous bilateral Wilms tumors (25.5 mo).

A study by Heck et al looked to determine whether the risk of childhood cancers among Hispanic children varies by maternal birthplace. The researchers found that for certain cancer types, such as glioma and astrocytoma, solid neuroblastoma, and Wilms tumor of the kidney, children of non–US born Hispanic mothers had the lowest risk.

## **Common Chemotherapy Drugs for Wilms Tumor**

| **Drug** | **Role in Treatment** | **Common Side Effects** |
| --- | --- | --- |
| Vincristine | Core drug in most regimens; disrupts microtubule formation to inhibit cell division | - Peripheral neuropathy (numbness, tingling, constipation)  - Hair loss  - Mild bone marrow suppression |
| Dactinomycin (Actinomycin D) | Core drug; intercalates DNA to inhibit RNA synthesis | - Bone marrow suppression (low blood counts)  - Nausea, vomiting  - Mouth sores (mucositis) |
| Doxorubicin | Added for higher risk or advanced tumors; anthracycline antibiotic causing DNA damage | - Cardiotoxicity (heart damage, dose-dependent)  - Hair loss  - Nausea, vomiting  - Mouth sores |
| Cyclophosphamide | Used in high-risk or recurrent disease; alkylating agent causing DNA crosslinks | - Bone marrow suppression  - Hemorrhagic cystitis (bladder irritation/bleeding)  - Nausea, vomiting |
| Etoposide | Used in advanced or recurrent tumors; topoisomerase II inhibitor | - Bone marrow suppression  - Hair loss  - Nausea, vomiting  - Risk of secondary leukemia (rare) |
| Carboplatin | Used in high-risk or recurrent cases; platinum-based DNA crosslinker | - Bone marrow suppression  - Kidney toxicity  - Hearing loss (ototoxicity) |
| Ifosfamide | Sometimes used in recurrent disease; alkylating agent similar to cyclophosphamide | - Bone marrow suppression  - Hemorrhagic cystitis  - Neurotoxicity (confusion, seizures) |
| Irinotecan | Occasionally used in recurrent disease; topoisomerase I inhibitor | - Diarrhea  - Bone marrow suppression  - Nausea, vomiting |
| Topotecan | Used in some protocols for recurrent disease; topoisomerase I inhibitor | - Bone marrow suppression  - Nausea, vomiting  - Diarrhea |

## Treatment Context

* Low-risk Wilms tumor: Usually treated with surgery followed by chemotherapy with vincristine and dactinomycin (AV regimen) for about 27 weeks.
* Intermediate-risk: May add doxorubicin to AV regimen.
* High-risk or advanced-stage tumors: More intensive chemotherapy including etoposide, carboplatin, cyclophosphamide, and doxorubicin, often combined with radiotherapy. Treatment duration can be up to 34 weeks or longer.
* Chemotherapy may be given before surgery (neoadjuvant) to shrink tumors or after surgery (adjuvant) to eliminate residual disease.

## **Major Genes Involved**

* WT1 (Wilms Tumor 1)
  + Located on chromosome 11p13, *WT1* is a tumor suppressor gene mutated in about 20% of Wilms tumors.
  + Both germline and somatic mutations occur; germline *WT1* mutations are strongly associated with bilateral Wilms tumor and predisposition syndromes.
  + *WT1* mutations often coincide with loss of heterozygosity (LOH) at 11p15.5, leading to abnormal expression of imprinted genes like *IGF2*.
* WTX (AMER1)
  + Located on the X chromosome (Xq11.1), *WTX* mutations occur in roughly 15-20% of tumors and partly overlap with *WT1* and *CTNNB1* mutations.
  + *WTX* is involved in the WNT/β-catenin signaling pathway.
* CTNNB1 (β-catenin)
  + Mutations in *CTNNB1* affect the WNT signaling pathway and occur in a subset of tumors, often alongside *WT1* mutations.
* Other Predisposition Genes
  + Recent studies have identified additional Wilms tumor predisposition genes, including TRIM28, FBXW7, KDM3B, NYNRIN, and others, accounting for about 10% of cases.
  + These genes are involved in diverse biological processes such as chromatin remodeling, ubiquitination, and transcription regulation.

## Epigenetic Alterations

* 11p15.5 Imprinting Abnormalities
  + Altered DNA methylation at imprinting control regions (e.g., *H19* and *KCNQ1OT1*) leads to abnormal expression of growth-regulating genes like *IGF2*.
  + These epigenetic changes are common (~70% of tumors) and are early events in tumorigenesis.
  + Paternal uniparental disomy (copy-neutral LOH) at 11p15.5 is frequently observed, especially in bilateral tumors.

## **Outlook / Prognosis**

The outlook for someone with Wilms tumor is generally good for almost all stages of Wilms tumor. It’s best when your healthcare provider is able to remove the tumor entirely and no cancer is found elsewhere in your child's body. There is a chance that Wilms tumor can come back (recur).

Although Wilms tumor can be treated successfully by a combination of surgery and chemotherapy and/or radiation, it’s still cancer. It can still be fatal.

#### **survival rate for Wilms tumor**

About 90% of people diagnosed with Wilms tumor are still alive five years later. The rates may be higher or lower depending on the stage and other factors like tumor size and how the cancer cells appear under a microscope (histology). At one point, children younger than 2 years old had a lower relapse rate, but age is less a factor today than it used to be.

## **Prevention**

There’s nothing you or your child can do to cause or prevent Wilms tumor.

### **When should I see my healthcare provider about Wilms tumor?**

If your child is being treated for Wilms tumor, you should contact your healthcare provider with any concerns. You should watch especially for any type of new symptom or if something seems to be getting worse.

During treatment, your healthcare team will let you know what things you should watch for, such as signs of urinary tract infections. This may require a trip to the emergency room.

You’ll probably need to make regular follow-up visits to make sure your child is staying healthy. Your provider may suggest your child sees a nephrologist (kidney specialist) or urologist (urinary tract specialist).

### **How can I help to keep my child healthy after treatment for Wilms tumor?**

Your child should:

* Drink adequate liquids to help keep the kidneys working well.
* Limit the use of drugs like aspirin, ibuprofen and naproxen. Talk with your child’s healthcare provider about which products are least likely to harm their kidneys.
* Have regular blood pressure checks.

## **Common Questions**

### **Is Wilms tumor painful?**

Wilms tumor can be painful in some cases.

### **What’s the difference between Wilms tumor (nephroblastoma) and neuroblastoma?**

Although the two terms look similar, they refer to cancer that starts in two different kinds of cells. Nephroblastoma is kidney cancer. Neuroblastoma is a cancer that starts in nerve cells, often in the adrenal glands but may invade a kidney. Both types of cancer affect children and both may show up as swollen spots in the abdomen.

**STAGING**

Stage I indicates the tumor was completely contained within the kidney without any breaks or spillage outside the renal capsule and no vascular invasion. This stage accounts for 40% to 45% of all Wilms tumors.

Stage II would be a tumor that has grown outside the kidney to some degree, such as into surrounding fatty tissue. Usually, the tumor would be completely removable by surgery, and regional lymph nodes are negative. About 20% of all Wilms tumors are at this stage.

Stage III comprises about 20% to 25% of all Wilms tumors and indicates a tumor which could not be completely removed surgically such as the following:

* Cancer has spread to the regional lymph nodes but not to more distant nodes, such as in the chest
* Cancer has grown into nearby vital structures so it could not be surgically removed completely
* Deposits of the tumor (tumor implants) are found in the peritoneum, or there are positive surgical margins
* Cancer cells were accidentally “spilled” into the abdominal cavity during surgery
* The tumor was removed in separate pieces surgically; such as one piece from the kidney and another from the adrenal gland
* A renal biopsy of the tumor was done before it was surgically removed

Stage IV tumors are those that have spread through the vascular system to distant organs such as the lungs, liver, brain, or bones, or to distant lymph nodes. These account for about 10% of all Wilms tumors.

Stage V are those cases where both kidneys are involved with tumor at the time of initial diagnosis. About 5% of all Wilms tumors are at this stage. Individual staging of each renal unit is needed as well.

**Doctor-patient conversation regarding Wilms tumor (nephroblastoma)**

Doctor: "Your child has been diagnosed with Wilms tumor, which is a type of kidney cancer that most commonly affects young children. I want to explain what this means, the treatment options, and answer any questions you have."

Parent: "What exactly is Wilms tumor? How serious is it?"

Doctor: "Wilms tumor is a cancer that arises from immature kidney cells. It is one of the most common kidney cancers in children and, importantly, has a very good prognosis with proper treatment. Most children can be cured, especially when the tumor is detected early."

Parent: "What tests have been done so far, and do we need more?"

Doctor: "We have done imaging studies like ultrasound and CT scans to see the size and extent of the tumor. Blood and urine tests have also been done to check overall health. Sometimes, we do additional scans to check if the tumor has spread. We may also do genetic testing to understand if there is any inherited risk."

Parent: "What are the treatment options? Will my child need surgery?"

Doctor: "Treatment usually involves a combination of surgery to remove the affected kidney and chemotherapy to kill any remaining cancer cells. Sometimes, chemotherapy is given before surgery to shrink the tumor. Radiation therapy is reserved for more advanced cases. The exact plan depends on the stage of the tumor and other factors."

Parent: "What side effects should we expect from treatment?"

Doctor: "Chemotherapy can cause side effects like nausea, hair loss, and low blood counts, which increase infection risk. Surgery carries risks but is generally safe when done by experienced pediatric surgeons. We will monitor your child closely and provide supportive care to manage side effects."

Parent: "How long will treatment last? What about follow-up?"

Doctor: "Treatment typically lasts several months, depending on the tumor stage and response. After treatment, your child will have regular follow-up visits for years to monitor for recurrence and manage any late effects."

Parent: "Who will be on the treatment team?"

Doctor: "Your child will be cared for by a multidisciplinary team including pediatric oncologists, surgeons, radiologists, nurses, social workers, and other specialists to support your family throughout treatment."

Parent: "Should we get a second opinion?"

Doctor: "Second opinions are common and encouraged. I can help you connect with specialized centers if you wish."

Parent: "What can we do to prepare for treatment?"

Doctor: "We will provide detailed instructions about hospital visits, medications, and supportive care. Emotional support is also important, and we can connect you with counseling and support groups."

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## 

## **Hepatoblastoma**

Hepatoblastoma (pronounced “heh-puh-tow-blas-tow-mah”) is a very rare liver cancer. Only 1 to 2 children in 1 million children in the U.S. have it. This condition typically affects children ages 1 to 3. Early diagnosis and surgery to remove the cancerous tumor(s) may cure it. A liver transplant is another option.

## **Symptoms and Causes**

Common hepatoblastoma symptoms include:

* Abdominal (belly) pain
* Lump in the middle or upper right side of your child’s belly (abdomen)
* Loss of appetite and unexplained weight loss
* Persistent nausea and vomiting
* Yellow-colored skin or eyes from jaundice

Hepatoblastomas grow very slowly. Your child may not have symptoms until the tumor is large enough to affect their body. For example, your child may have belly pain that doesn’t go away or appear to be losing weight. Chances are, hepatoblastoma isn’t the reason why your child has a stomachache. Your intuition may be telling you that your child’s touchy tummy is a serious issue. In that case, don’t hesitate to call their pediatrician.

### **Hepatoblastoma causes**

Experts don’t know exactly what causes healthy liver cells to become cancer cells. But there are conditions that increase hepatoblastoma risk:

* Very low birth weight (birth weight below 5 pounds, 5 ounces or 2,408 grams)
* Preterm birth (being born at 37 weeks gestation)
* Aicardi syndrome, which causes malformations in your child’s brain and other parts of their body
* Beckwith-Wiedemann syndrome that can affect your child’s growth and increase their risk of cancer
* Biliary atresia, which blocks babies’ bile ducts and damages their livers
* Edwards syndrome (trisomy 18) that affects how your child’s body develops and grows
* Familial adenomatous polyposis (FAP), which causes large numbers of precancerous polyps (growths) in your colon
* Hemihyperplasia that causes one side of your child’s body to grow faster than the other
* Simpson-Golabi-Behmel syndrome (SGB) that causes abnormalities in children’s liver and other organs

### **Complications of hepatoblastoma**

Cancer treatments for hepatoblastoma may cause late effects. These are health issues that surface months and years after diagnosis or treatment. Your child may need long-term follow-up and medical care to manage them.

Second cancers are examples of a late effect. This is a new type of cancer. It appears months or years after your child completes hepatoblastoma treatment.

Late effects may make an impact on your child’s:

* Ability to think, learn and remember information
* Growth and development
* Moods, feelings and mental health
* Organs and tissues

## **Diagnosis and Tests**

Your child’s pediatrician will do a physical examination. They’ll ask about your child’s symptoms and when you first noticed symptoms. They may do some of the following tests:

* Alpha-fetoprotein (AFP) tests. AFP is a substance produced by your child’s liver.
* Complete blood count (CBC). This test measures and counts the blood cells in your child’s blood.
* Comprehensive metabolic panel (CMP). A CMP tests your child’s blood for 14 different substances and liver function.
* Liver and Doppler ultrasounds. Healthcare providers use these tests to get images of the inside of your child’s liver.
* Magnetic resonance imaging (MRI). This test produces very clear images of the organs and blood vessels.
* Vascular ultrasound. Providers do this test to see the network of blood vessels that enter and leave your child’s liver.

Your child’s pediatrician may refer you to a pediatric oncologist. This is a doctor with experience treating cancer in children.

### **Stages of hepatoblastoma**

Cancer staging is how oncologists set treatment plans. Pediatric oncologists use two grouping systems instead of cancer stages. Those groups are:

* PRETEXT stands for “pre-treatment extent of disease.” It refers to how cancer affects your child’s liver before pre-surgery chemotherapy. Your child’s pediatric oncologist looks for the number of tumors. They also check the tumor(s) size and appearance
* POSTTEXT refers to “post-treatment extent of disease” after pre-surgery treatment.

Your liver has two lobes. Oncologists divide the two lobes into four groups. They classify each group by the number of liver sections with tumors. The more sections with tumors, the higher the group number.

Here’s an example: Tests detect two tumors in different sections of your child’s liver. That puts the cancer in PRETEXT Group II. If pre-surgery chemotherapy removes one tumor, the cancer is POSTEXT Group I. Your child’s oncologist may say your child now has Group I hepatoblastoma. Other hepatoblastoma groups are:

* Group I. There’s cancer in one section of your child’s liver but none in the three other sections.
* Group II. This group has two scenarios. In one, there’s cancer in two sections of the liver that are next to each other, but not in the other two sections. In the other, there’s cancer in one section, but not in two sections that are next to each other.
* Group III. One or more sections of the liver contain cancer. But there isn’t cancer in the sections that are right next to those with cancer.
* Group IV. There’s cancer in all four sections of your child’s liver.

#### **Specific treatments and procedures**

The most common treatment is surgery to remove the part of your child’s liver that cancer affects. The liver is the only organ that can grow back after surgery. That means your child’s liver will eventually grow back to its original size.

Your child’s pediatric oncologist may do more chemotherapy before and after surgery. They do this treatment to shrink the tumor.

Your child may receive chemotherapy for four to six weeks after surgery. Chemotherapy after surgery reduces the chance that cancer will come back.

Other hepatoblastoma treatments include:

* Ablation therapy is a minimally invasive procedure for hepatoblastoma that comes back.
* Liver transplant is an option if cancer affects the central part of your child’s liver or many sections of their liver.
* Transarterial chemoembolization (TACE) cuts off the tumor’s blood supply and delivers chemotherapy directly to the tumor.

## **Outlook / Prognosis**

Yes, but it depends on when your child is diagnosed and receives treatment. Your child’s surgeon may be able to cure hepatoblastoma if they can remove the entire tumor or all of the tumors.

#### **Hepatoblastoma survival rates**

Cancer survival rates are estimates based on people’s experiences with different kinds of cancer. Overall, 4 out of 5 children with hepatoblastoma will be alive five years after diagnosis.

When you think about survival rates, it’s important to keep in mind that your child’s experience with hepatoblastoma may be different from what other children experience.

Many things can make a difference in hepatoblastoma. If you have questions about survival rates, your child’s pediatric oncologist is your best resource for information. They’ll explain what survival rate data means in your child’s case.

#### **When should my child see their healthcare provider?**

Your child should have regular follow-up appointments with their cancer care team. The team will check your child’s health, including any late effect health issues. Team members will look for signs of returning hepatoblastoma or a new cancer.

Hepatoblastoma treatment typically involves surgery. Surgery can have complications, including infection. You should take your child to the emergency room if they:

* Have a fever that’s higher than 100.4 degrees Fahrenheit (38.3 degrees Celsius)
* The surgery site turns dark red, or your child says it hurts when you touch it
* There are green or yellow substances oozing from the surgery site

## **Common Questions**

### **What can I do to help my child manage hepatoblastoma tests and treatment?**

Tests are essential to find out why your child is sick. But needles for blood tests can sting. MRI machines make loud scary noises. Your child may feel anxious about having chemotherapy or surgery. These are very normal reactions when a child has cancer. Working with a child life specialist may help your child (and you) get through tests and treatment.

## **Epidemiology**

### United States data

Hepatoblastoma accounts for 79% of all liver tumors in children and almost two thirds of primary malignant liver tumors in the pediatric age group. Approximately 100 cases of hepatoblastoma are reported per year. The annual incidence of hepatoblastoma in infants younger than 1 year is 11.2 cases per million; in 1990-1995, the annual incidence in children overall was 1.5 cases per million, which is almost double the incidence from 1975-1979.

A significantly higher rate of hepatoblastomas is observed among low birth weight (LBW) and very low birth weight (VLBW) infants born prematurely.

A Children’s Oncology Group (COG) protocol (AEP104C1) is investigating exogenous and endogenous causes for the increase in incidence and potential cause of premature births. The study is also exploring potential effectors independent of prematurity and LBW or VLBW. All children with hepatoblastoma diagnosed before age 6 years from 2000-2005 are eligible for retrospective analysis, and prospective analysis will be performed for children diagnosed between June 2005 and December 31, 2008. This is the largest, most comprehensive case-control study of hepatoblastoma performed thus far.

### International data

In Japan, efforts to improve vaccination rates have led to decreases in hepatocellular carcinoma (HCC) and, to a lesser degree, in hepatoblastoma. Carcinogen exposure in some developing countries is linked to hepatoblastoma and HCC.

### Race-, sex-, and age-related demographics

White children are affected almost 5 times more frequently than Black children. Black patients tend to have worse outcomes.

Males are typically affected more frequently than females; the male-to-female ratio is 1.7:1. Male-to-female ratios are somewhat higher in Europe (1.6-3.3:1) and Taiwan (2.9:1).

Hepatoblastoma usually affects children younger than 3 years, and the median age at diagnosis is 1 year. Hepatoblastoma is very rarely diagnosed in adolescence and is exceedingly rare in adults. Occasionally, nests of hepatoblastoma cells are found in hepatocellular carcinoma lesions; this is more common in adults than in children. Older children and adults tend to have a worse prognosis

**DIFFERENTIAL DIAGNOSIS**

* Hepatic mesenchymal hamartoma
  + A benign tumor of infancy with cystic and solid components; usually has different imaging features and normal AFP levels.
* Infantile hemangioma / hemangioendothelioma
  + Vascular tumors of the liver; often present with different enhancement patterns on imaging and may cause high-output cardiac failure.
* Hepatocellular carcinoma (HCC)
  + Rare in young children but can resemble hepatoblastoma, especially the macro trabecular subtype; usually occurs in older children or those with underlying liver disease.
* Metastatic tumors to the liver
  + Neuroblastoma metastases are common in children and can mimic primary liver tumors.
* Rhabdomyosarcoma
  + Rare primary liver tumor or metastatic disease.
* Teratoma
  + Contains multiple tissue types; rare in the liver.
* Undifferentiated sarcoma
  + Aggressive liver tumor with distinct histology.
* Wilms tumor with liver metastases
  + Can present as liver masses in children with known Wilms tumor.
* Focal nodular hyperplasia (FNH) and hepatic adenoma
  + Benign liver lesions, rare in infants but part of DDx in older children.
* Lymphoma involving the liver
  + May present with hepatic masses.

## **Genetic Features:**

* APC Gene Mutations and Familial Adenomatous Polyposis (FAP):
  + Germline mutations in the *APC* gene, which cause FAP, are strongly associated with hepatoblastoma development, especially in boys.
  + Mutations cluster in the 5’ region of *APC*, but the mutation site does not reliably predict hepatoblastoma risk within FAP families.
* Somatic Mutations:
  + *CTNNB1* (β-catenin) mutations are frequent and are considered a hallmark of hepatoblastoma, affecting the Wnt/β-catenin signaling pathway.
  + *TERT* promoter mutations and other driver mutations occur but are less common.
* Germline Variants in Cancer Predisposition Genes:
  + Besides *APC*, pathogenic or likely pathogenic germline variants have been found in genes such as *TP53*, *BRCA2*, *CHEK2*, *DROSHA*, *ERCC5*, *FAH*, *MSH2*, *ATM*, and others involved in DNA repair and genome stability.
  + These germline mutations may confer increased cancer risk and influence tumor development.

## Epigenetic Alterations:

* DNA Methylation:
  + Hepatoblastoma tissues show global hypomethylation alongside hypermethylation of tumor suppressor gene promoters (e.g., *APC*, *RASSF1A*, *CDH1*), contributing to tumorigenesis.
  + These epigenetic changes are significant in hepatoblastoma biology and may correlate with prognosis.
* Non-coding RNA and SNPs:
  + Polymorphisms in the long non-coding RNA *H19* gene and m^6A RNA modification genes (*WTAP*, *YTHDF1*, *YTHDC1*, *ALKBH5*) have been linked to hepatoblastoma risk and progression, suggesting a role for RNA regulation in tumor development

**Doctor-patient conversation about hepatoblastoma**,

Doctor: "Your child has been diagnosed with hepatoblastoma, which is the most common liver cancer in young children, usually occurring before the age of 3. I want to explain what this means, the treatment options available, and answer any questions you have."

Parent: "What exactly is hepatoblastoma? How serious is it?"

Doctor: "Hepatoblastoma is a malignant tumor that arises from immature liver cells. The good news is that with modern treatment—including chemotherapy and surgery—many children can be cured. The prognosis depends on how much of the liver is involved and whether the tumor has spread."

Parent: "What tests have been done so far, and do we need more?"

Doctor: "We have done imaging studies like ultrasound, CT, and MRI to evaluate the size and location of the tumor and to check if it has spread within the liver or to other organs. We also check blood tests, including alpha-fetoprotein (AFP), which is often elevated in hepatoblastoma. Sometimes additional scans or biopsy samples are needed to guide treatment."

Parent: "What are the treatment options? Will my child need surgery?"

Doctor: "Treatment usually starts with chemotherapy to shrink the tumor. After that, surgery is performed to remove the tumor or part of the liver. In some cases where the tumor cannot be removed safely, a liver transplant may be necessary. After surgery, chemotherapy is often given again to kill any remaining cancer cells."

Parent: "What side effects should we expect from treatment?"

Doctor: "Chemotherapy can cause side effects like nausea, vomiting, hair loss, and low blood counts, which increase infection risk. Surgery carries risks but is generally safe when done by experienced pediatric surgeons. We will closely monitor your child and provide supportive care to manage side effects."

Parent: "How long will treatment last? What about follow-up?"

Doctor: "Treatment typically lasts several months, depending on the tumor stage and response. After treatment, your child will have regular follow-up visits with blood tests and imaging to monitor for recurrence and manage any long-term effects."

Parent: "Who will be on the treatment team?"

Doctor: "Your child will be cared for by a multidisciplinary team including pediatric oncologists, surgeons, radiologists, pathologists, nurses, and social workers. This team will support your child and family throughout treatment and recovery."

Parent: "Should we get a second opinion?"

Doctor: "Second opinions are common and encouraged. I can help you connect with specialized centers if you wish."

Parent: "What can we do to prepare for treatment?"

Doctor: "We will provide detailed instructions about hospital visits, medications, and supportive care. Emotional support is also important, and we can connect you with counseling and support groups."

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**MEDULLOBLASTOMA**

**DEFINITION AND DESCRIPTION**

Medulloblastoma (muh-dul-o-blas-TOE-muh) is a cancerous brain tumor that starts in the lower back part of the brain. This part of the brain is called the cerebellum. It is involved in muscle coordination, balance and movement.

Medulloblastoma begins as a growth of cells, which is called a tumor. The cells grow quickly and can spread to other parts of the brain. Medulloblastoma cells tend to spread through the fluid that surrounds and protects your brain and spinal cord. This is called cerebrospinal fluid. Medulloblastomas don't usually spread to other parts of the body.

Medulloblastoma can happen at any age, but most often occurs in young children. Though medulloblastoma is rare, it's the most common cancerous brain tumor in children. Medulloblastoma happens more often in families that have a history of conditions that increase the risk of cancer. These syndromes include Gorlin syndrome or Turcot syndrome.

**SYMPTOMS**

Medulloblastoma symptoms happen when the cancer grows or causes pressure to build up in the brain. Signs and symptoms of medulloblastoma may include:

* Dizziness.
* Double vision.
* Headaches.
* Nausea.
* Poor coordination.
* Tiredness.
* Unsteady walk.
* Vomiting.

### **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 not clear what causes medulloblastoma. This cancer starts as a growth of cells in the brain.

Medulloblastoma happens when cells in the brain 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 grow and multiply quickly. Cancer cells can keep living when healthy cells die. This causes too many cells.

The cancer cells form a mass called a tumor that can grow to push on nearby structures. The cancer cells can invade and destroy healthy body tissue. They also can spread to other areas.

**Risk factors**

Factors that may increase the risk of medulloblastoma include:

* **Young age.** Medulloblastoma can happen at any age. This cancer happens most often in children.
* **Inherited syndromes.** Medulloblastoma happens more often in families that have a history of conditions that increase the risk of cancer. These conditions include Fanconi anemia, Gorlin syndrome, Li-Fraumeni syndrome, Rubinstein-Taybi syndrome and Turcot syndrome.

## **Diagnosis**

The process of diagnosis usually starts with a medical history review and a discussion of signs and symptoms. Tests and procedures used to diagnose medulloblastoma include:

* **Neurological exam.** During this exam, vision, hearing, balance, coordination and reflexes are tested. This can help show which part of the brain might be affected by the tumor.
* **Imaging tests.** Imaging tests capture pictures of the brain. The pictures can show the size and location of the tumor. These tests may show pressure or blockages of the cerebrospinal fluid. CTs and MRIs are used for the imaging, but other tests might be needed in certain situations.
* **Tissue sample testing.** A biopsy is a procedure to remove a sample of the tumor for testing. Biopsies for medulloblastoma are uncommon but might be used in certain situations. In a biopsy, part of the skull is removed. A needle is used to take a sample of the tumor. The sample is tested in a lab to see if it's a medulloblastoma.
* **Removal of cerebrospinal fluid for testing.** A spinal tap, also called a lumbar puncture, involves inserting a needle between two bones in the lower spine. The needle draws out cerebrospinal fluid from around the spinal cord. The fluid is tested in a lab to look for tumor cells. This test is only done after managing the pressure in the brain or removing the tumor.

**Treatment**

Treatment for medulloblastoma usually includes surgery followed by radiation or chemotherapy, or both. Your healthcare team considers many factors when creating a treatment plan. These factors might include the tumor's location, how fast it's growing, whether it has spread to other parts of the brain and the results of tests on the tumor cells. Your care team also considers your age and your overall health.

Treatment options include:

* **Surgery to relieve fluid buildup in the brain.** A medulloblastoma may grow to block the flow of cerebrospinal fluid. This can cause a buildup of fluid that puts pressure on the brain. To reduce the pressure, a surgeon can create a pathway for the fluid to flow out of the brain. Sometimes this procedure can be combined with surgery to remove the tumor.
* **Surgery to remove the medulloblastoma.** The goal of surgery is to remove all of the medulloblastoma. But sometimes it's not possible to fully remove the tumor because it forms near important structures deep within the brain. Most people with medulloblastoma need more treatments after surgery to kill any cancer cells that are left.
* **Radiation therapy.** Radiation therapy uses powerful energy beams to kill cancer cells. The energy can come from X-rays, protons and other sources. During radiation therapy, a machine directs beams of energy to specific points on the body. Radiation therapy is often used after surgery.
* **Chemotherapy.** Chemotherapy uses medicines to kill cancer cells. Typically, children and adults with medulloblastoma receive these medicines as an injection into veins. Chemotherapy may be used after surgery or radiation therapy. Sometimes it's done at the same time as radiation therapy.

## **Outlook / Prognosis**

Your team of medical experts may include:

* Medical oncologists
* Neurosurgeons
* Pathologists
* Physical therapists
* Radiologists
* Radiation oncologists
* Neuropsychologists

They’ll create a personalized treatment plan according to your specific needs.

#### **Can you survive medulloblastoma?**

In many cases, yes. While medulloblastoma has the potential to spread throughout your entire nervous system, many people can be cured. There’s a higher chance of survival if the medulloblastoma hasn’t spread to other parts of your brain and spinal cord.

#### **Prognosis for medulloblastoma**

The five-year medulloblastoma survival rate is over 80%. This means that over 80% of all people diagnosed with medulloblastoma are still alive five years later. Researchers base these numbers on medulloblastoma outcomes in the past.

But keep in mind, survival rates can’t tell you what will happen in your situation. To better understand survival rates and what they mean for you, talk to your healthcare provider

## **Differential Diagnoses**

* Brainstem Gliomas
* Cavernous Sinus Syndromes
* Cerebellar Hemorrhage
* Cerebral Aneurysm
* Glioblastoma
* Hydrocephalus
* Oligodendroglioma Imaging
* Low-Grade Astrocytoma
* Pediatric Craniopharyngioma
* Pediatric Ependymoma
* Tolosa-Hunt Syndrome
* Ependymoma
* Pilocytic astrocytoma
* Atypical teratoid/rhabdoid tumor (AT/RT)
* Hemangioblastoma
* Craniopharyngioma
* Pineal region tumors (pinealoma)
* Primary CNS lymphoma
* Meningioma
* Schwanno
* Pituitary adenoma
* Arteriovenous (AV) malformation
* Brain aneurysm
* Bacterial brain abscess
* Tuberculosis
* Toxoplasmosis
* Hydatid cyst
* CNS cryptococcosis
* CNS aspergillosis
* Brain metastasis

## **Epidemiology**

### United States statistics

Approximately 250 new patients are diagnosed annually. Among pediatric patients aged 0-14 years, medulloblastomas represent 68.8% of all embryonal tumors.

### International statistics

Exact figures are unknown. In general, brain tumors occur at a rate of 2.5-4 per 100,000 at-risk children per year. Of these, approximately 18% are medulloblastoma.

### Race-, sex-, and age-related demographics

No racial predisposition is noted. Data from the Surveillance, Epidemiology, and End Results (SEER) program showed that patients aged 0-14 years in the United States have an incidence rate per million population of 5.7 in Whites and 5 in Blacks.

US incidence per 1 million population for patients aged 0-14 years is 6.1 for boys and 4.5 for girls.

Peak age of incidence is during the first decade of life. Approximately 80% of patients are diagnosed in the first 15 years of life.

## **Common Chemotherapy Drugs Used in Medulloblastoma Treatment**

| **Drug** | **Role** | **Common Side Effects** |
| --- | --- | --- |
| Cisplatin | Platinum-based agent; key drug in induction and maintenance chemotherapy | - Nephrotoxicity (kidney damage)  - Ototoxicity (hearing loss)  - Nausea and vomiting  - Peripheral neuropathy |
| Vincristine | Microtubule inhibitor; given weekly or multiple times per cycle | - Peripheral neuropathy (numbness, tingling, constipation)  - Hair loss  - Mild bone marrow suppression |
| Lomustine (CCNU) | Alkylating agent; used in maintenance chemotherapy | - Bone marrow suppression (delayed)  - Nausea  - Pulmonary toxicity (rare) |
| Cyclophosphamide | Alkylating agent; used in high-dose and maintenance regimens | - Bone marrow suppression  - Hemorrhagic cystitis (bladder irritation)  - Nausea, vomiting |
| Carboplatin | Platinum agent sometimes used during radiation or in high-risk cases | - Bone marrow suppression  - Nephrotoxicity (less than cisplatin)  - Ototoxicity (less than cisplatin) |
| Topotecan | Topoisomerase I inhibitor; used in dose-intense regimens | - Bone marrow suppression  - Nausea, vomiting  - Diarrhea |
| Mesna | Protective agent given with cyclophosphamide to prevent hemorrhagic cystitis | - Generally well tolerated; used to reduce bladder toxicity |
| G-CSF (filgrastim) | Growth factor to stimulate white blood cell recovery after chemotherapy | - Bone pain  - Injection site reactions |

## Typical Chemotherapy Regimens

* Standard-risk medulloblastoma:
  + Regimen A: Lomustine (Day 0), Cisplatin (Day 1), Vincristine (Days 1, 7, 14) repeated every 42 days for 8 cycles.
  + Regimen B: Cisplatin (Day 1), Vincristine (Days 1, 7, 14), Cyclophosphamide (Days 21, 22) every 42 days for 8 cycles.
* High-risk medulloblastoma:
  + Carboplatin and vincristine during radiation therapy.
  + Maintenance chemotherapy with cisplatin, lomustine, vincristine, and cyclophosphamide in 6 cycles every 28 days.
  + Mesna administered with cyclophosphamide to prevent bladder toxicity.
  + G-CSF given post-chemotherapy to aid neutrophil recovery.
* Dose-intense chemotherapy with stem cell support:
  + Cisplatin, vincristine, cyclophosphamide with peripheral blood stem cell infusion and G-CSF support.

## **GENOMIC DATA**

## WNT Subgroup

* Characterized by activation of the WNT signaling pathway, often due to mutations in the CTNNB1 gene (encoding β-catenin).
* Frequently shows monosomy of chromosome 6.
* Patients typically have a favorable prognosis with high survival rates.
* Occurs in older children and adolescents less commonly in infants.

## 2. SHH (Sonic Hedgehog) Subgroup

* Driven by aberrations in the SHH signaling pathway, including mutations in PTCH1, SUFU, SMO, and sometimes TP53.
* Includes desmoplastic/nodular histology and is more common in infants and adults.
* Prognosis is intermediate and depends on age and TP53 mutation status.
* Subclassified further into subtypes (e.g., SHHα, SHHβ) with distinct clinical outcomes.

## 3. Group 3

* Often associated with MYC amplification, a marker of high-risk disease.
* Frequently presents with metastatic disease at diagnosis.
* Has the poorest prognosis among the subgroups.
* Molecular drivers are less well defined but include alterations in chromatin regulation genes.

## 4. Group 4

* The most common subgroup, representing about 35% of cases.
* Characterized by isochromosome 17q (i17q) and other chromosomal aberrations.
* Intermediate prognosis; some cases present with metastases.
* Molecular drivers are less clearly understood but overlap with Group 3 features

## **Doctor-Patient Conversation: Medulloblastoma**

## DOCTOR;“Thank you for coming in today. I want to talk with you about the diagnosis we have for your child. The tests show that your child has a medulloblastoma, which is a type of brain tumor that arises in the cerebellum, the part of the brain that controls balance and coordination.”

Parent:  
“That sounds serious. What exactly is medulloblastoma? Is it cancer?”

Doctor:  
“Yes, it is a malignant brain tumor, but it’s important to know that medulloblastoma is one of the most common brain tumors in children, and with modern treatment, many children can be successfully treated. We have several treatment options that we will tailor to your child’s specific case.”

Parent:  
“What caused this? Is it genetic? Will it affect other family members?”

Doctor:  
“Medulloblastoma can arise due to a combination of genetic and environmental factors. Some children have specific genetic changes in the tumor cells that we can identify, which help us understand how aggressive the tumor is and guide treatment. Most cases are not inherited, but we can discuss genetic counseling if needed.”

Parent:  
“What treatments will my child need? What does the process look like?”

Doctor:  
“Treatment usually involves three main parts: surgery to remove as much of the tumor as possible, followed by radiation therapy to the brain and spine to kill remaining cancer cells, and chemotherapy to further reduce the risk of recurrence. The exact plan depends on the tumor’s molecular subgroup, your child’s age, and overall health.”

Parent:  
“What are the side effects? How will this affect my child’s daily life?”

Doctor:  
“Side effects vary depending on the treatment phase. Surgery may cause temporary balance or coordination issues. Radiation and chemotherapy can cause fatigue, nausea, hair loss, and increased risk of infections. We will provide supportive care to manage these. Long-term, some children may experience effects on learning or hearing, so we will monitor and support your child closely.”

Parent:  
“How long will treatment last? What about follow-up care?”

Doctor:  
“Treatment typically lasts several months. After therapy, your child will have regular follow-up visits with imaging and exams to monitor for any signs of recurrence and to manage any late effects. Our team will work with you throughout this process.”

Parent:  
“Who will be involved in my child’s care?”

Doctor:  
“You will have a multidisciplinary team including pediatric neurosurgeons, oncologists, radiation oncologists, nurses, therapists, social workers, and counselors to support your child and family.”

Parent:  
“Should we get a second opinion?”

Doctor:  
“Absolutely. Many families find it helpful to get a second opinion, especially from specialized pediatric brain tumor centers. I can help you with referrals if you wish.”

Parent:  
“What can we do to prepare for treatment?”

Doctor:  
“We will provide detailed guidance on hospital visits, medications, and supportive care. Emotional support is also important, and we can connect you with counseling and support groups.”

**QUESTION AND ANSWER SET**

## **Do I have a medulloblastoma?**

A definitive diagnosis requires imaging (MRI/CT) and biopsy or surgical pathology. If you have symptoms and imaging suggestive of medulloblastoma, further tests will confirm the diagnosis.

## **Will I need more tests?**

Yes. Additional tests often include:

* MRI of brain and spine to assess tumor extent and spread
* Molecular/genetic profiling of tumor tissue to classify subtype
* Lumbar puncture to check for tumor cells in cerebrospinal fluid
* Hearing and kidney function tests before treatment

## **Can my medulloblastoma be removed?**

Surgery aims to remove as much tumor as safely possible. Complete or near-total resection improves outcomes but may not always be feasible due to tumor location.

## **Why do I need additional treatments if surgery removes the entire medulloblastoma?**

Medulloblastoma cells can spread microscopically through the cerebrospinal fluid and central nervous system. Radiation and chemotherapy target residual microscopic disease to reduce recurrence risk.

## **What are the treatment options?**

* Surgery: Maximal safe tumor removal
* Radiation therapy: Craniospinal irradiation (CSI) plus boost to tumor bed; proton therapy to reduce side effects
* Chemotherapy: Regimens including vincristine, cisplatin, cyclophosphamide, lomustine, and others
* Targeted therapies: For specific molecular subtypes (e.g., SHH inhibitors)
* Clinical trials: Immunotherapy, vaccines, novel agents

## **What is the stage of my medulloblastoma?**

Staging depends on tumor size, extent of local invasion, and presence of metastases in brain/spinal fluid. Molecular subgroup classification (WNT, SHH, Group 3, Group 4) also informs prognosis and treatment.

## Has my medulloblastoma spread to other parts of my body?

Medulloblastoma primarily spreads within the central nervous system (brain and spinal cord). Spread outside the CNS is rare. Imaging and CSF analysis determine spread.

## **How much does each treatment increase my chances of a cure or prolong my life?**

* Surgery plus radiation and chemotherapy can achieve 5-year survival rates over 80% in standard-risk patients.
* Molecular sub group and presence of metastases influence prognosis.
* Targeted therapies and clinical trials may improve outcomes further.

## **What are the potential side effects of each treatment?**

* Surgery: Risks include neurological deficits, posterior fossa syndrome
* Radiation: Fatigue, hair loss, neurocognitive effects, hearing loss (proton therapy reduces some risks)
* Chemotherapy: Nausea, vomiting, bone marrow suppression, hearing loss, neuropathy
* Targeted therapies: Vary by agent; generally fewer systemic effects

## **How will each treatment affect my daily life?**

Treatment involves hospital stays and outpatient visits, possible temporary side effects like fatigue and nausea, and may impact school and activities. Supportive care helps manage symptoms.

## **Is there one treatment option you believe is the best?**

A combined multimodal approach (surgery + radiation + chemotherapy) tailored to your tumor’s molecular subtype and risk profile offers the best chance of cure.

## What would you recommend to a friend or family member in my situation?

I would recommend treatment at a specialized pediatric neuro-oncology center with access to multidisciplinary care and clinical trials.

## **Should I see a specialist?**

Yes. Care by a pediatric neuro-oncologist, neurosurgeon, radiation oncologist, and supportive care team is essential.

## What will determine whether I should plan for a follow-up visit?

Follow-up is based on treatment milestones, symptom changes, and routine surveillance imaging schedules.

## **Will I need to continue coming back?**

Yes. Long-term follow-up is critical to monitor for tumor recurrence, late effects of treatment, and support rehabilitation.

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**MALE BREAST CANCER**

**DEFINITION AND DESCRIPTION**

Male breast cancer is a rare cancer that begins as a growth of cells in the breast tissue of men.

Breast cancer is typically thought of as a condition that happens in women. But everyone is born with some breast tissue. So anyone can get breast cancer.

Male breast cancer is rare. It happens most often in older men, though it can occur at any age.

Treatment for male breast cancer typically involves surgery to remove the breast tissue. Other treatments, such as chemotherapy and radiation therapy, may be recommended as well.

**Causes**

It's not clear what causes male breast cancer.

Male breast cancer starts when cells in the breast tissue 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.

### **Where breast cancer begins in men**

Everyone is born with a small amount of breast tissue. Breast tissue consists of milk-producing glands, ducts that carry milk to the nipples and fat.

During puberty, people assigned female at birth typically begin growing more breast tissue. People assigned male at birth generally do not grow more breast tissue. But because everyone is born with a small amount of breast tissue, breast cancer can develop in anyone.

Types of male breast cancer include:

* **Cancer that begins in the milk ducts, called ductal carcinoma.** This type of breast cancer starts in the tubes that connect to the nipple. These tubes are called ducts. Ductal carcinoma is the most common type of male breast cancer.
* **Cancer that begins in the milk-producing glands, called lobular carcinoma.** This type of cancer begins in the glands that have the potential to make breast milk. These glands are called lobules. Lobular carcinoma is less common in people assigned male at birth because they usually have fewer lobular cells.
* **Other types of cancer.** Other, rarer types of male breast cancer include Paget's disease of the nipple and inflammatory breast cancer.

**Risk factors**

Factors that increase the risk of male breast cancer include:

* **Older age.** The risk of breast cancer increases with age. Male breast cancer is most often diagnosed in men in their 60s.
* **Hormone therapy for prostate cancer or medicines containing estrogen.** If you take estrogen-related medicines, such as those used for hormone therapy for prostate cancer, your risk of breast cancer rises.
* **Family history of breast cancer.** If you have a blood relative with breast cancer, you have a greater chance of getting the disease.
* **Inherited DNA changes that increase breast cancer risk.** Some of the DNA changes that can lead to breast cancer are passed down from parents to children. People born with these DNA changes have a greater risk of breast cancer. For example, the DNA changes BRCA1 and BRCA2 increase the risk of male breast cancer.
* **Klinefelter syndrome.** This genetic syndrome occurs when males are born with more than one copy of the X chromosome. Klinefelter syndrome affects the development of the testicles. It causes changes in the balance of hormones in the body, which can increase the risk of male breast cancer.
* **Liver disease.** Certain conditions, such as cirrhosis of the liver, can change the balance of hormones in the body. This raises the risk of male breast cancer.
* **Obesity.** Obesity is linked with higher levels of estrogen in the body. This increases the risk of male breast cancer.
* **Testicle disease or surgery.** Having inflamed testicles, called orchitis, or surgery to remove a testicle, called orchiectomy, can increase the risk of male breast cancer.

**Symptoms**

Signs and symptoms of male breast cancer can include:

* A painless lump or thickening of the skin on the chest.
* Changes to the skin covering the chest, such as dimpling, puckering, scaling or changes in the color of the skin.
* Changes to the nipple, such as changes in the skin color or scaling, or a nipple that begins to turn inward.
* Discharge or bleeding from the nipple.

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

Make an appointment with a doctor or other health care professional if you have symptoms that worry you.

### **Diagnosing male breast cancer**

Tests and procedures to diagnose male breast cancer might include:

* **Clinical breast exam.** During this exam, a health care professional feels the breasts and surrounding areas for lumps or other changes. This exam helps the health professional understand how large the lumps are, how they feel, and how close they are to skin and muscles.
* **Imaging tests.** Imaging tests can create pictures of breast tissue to look for signs of cancer. Tests may include a breast X-ray, called a mammogram, an ultrasound or an MRI scan.
* **Removing a sample of breast cells for testing, called a biopsy.** To determine whether you have cancer, you might have a procedure to remove a sample of cells for testing in a lab. This procedure is called a biopsy. To get the sample, a health care professional puts a needle through the skin on your chest. The health professional guides the needle using a mammogram or another imaging test.  
  In the lab, specialists examine the cells under a microscope to see if they're cancer. Other tests can tell whether your cancer cells have hormone receptors or certain DNA changes. The test results help your health care team create a treatment plan.

There might be other tests and procedures depending on your situation.

### **Staging the cancer**

After confirming a diagnosis of breast cancer, your health care team works to find the extent of your cancer. This is called the cancer's stage. Your health care team uses your cancer's stage to understand your prognosis and to make a treatment plan.

Male breast cancer staging often involves imaging tests. The images can tell your health care team about your cancer's size and whether it has spread. Tests may include:

* Bone scan.
* CT scan.
* Positron emission tomography (PET) scan.

Results from lab tests on the cancer cells also help determine the cancer's stage. Tests might show the cancer's grade. This tells your health care team how quickly the cancer is growing. Your care team also considers whether your cancer cells have receptors. Tests can look for receptors for estrogen, progesterone and HER2.

Results from these tests are used to assign your cancer a stage. Breast cancer stages range from 0 to 4. Stage 0 means the cancer is very small. At this stage, the cancer is inside the milk ducts. It hasn't broken out into the breast tissue. Doctors sometimes call this noninvasive cancer.

As the cancer grows and invades the breast tissue, the stages get higher. Stage 4 breast cancer means the cancer has spread to other areas of the body.

**Treatment**

Male breast cancer treatment usually starts with surgery. Other common treatments include chemotherapy, hormone therapy and radiation therapy. To create a treatment plan, your health care team looks at your cancer's stage, your overall health and what you prefer.

### **Surgery**

The goal of surgery is to remove the cancer and some of the healthy tissue around it. Operations used to treat male breast cancer include:

* **Removing all the breast tissue, called a mastectomy.** A mastectomy involves removing all the breast tissue from one side of your chest. This includes removing the nipple and the skin around it, called the areola. This is the most common type of surgery for male breast cancer.
* **Removing the cancer and some healthy tissue, called lumpectomy.** A lumpectomy involves removing the cancer and some of the healthy tissue around it. The rest of the breast tissue isn't removed. Sometimes doctors call this breast-conserving surgery. Often, radiation therapy is recommended after lumpectomy.
* **Removing a few lymph nodes for testing, called a sentinel lymph node biopsy.** The surgeon removes the lymph nodes most likely to be the first place your cancer cells would spread. Those few lymph nodes, called sentinel nodes, are sent to a lab for testing.  
  If there are no cancer cells, there is a good chance that your breast cancer hasn't spread past your breast tissue. If cancer is found, more lymph nodes are removed for testing.

### **Radiation therapy**

Radiation therapy uses powerful energy beams to kill cancer cells. The energy can come from X-rays, protons or other sources. During radiation therapy, you lie on a table while a machine moves around you. The machine directs radiation to precise points on your body.

In male breast cancer, radiation therapy may be used after surgery to kill any cancer cells that might be left behind. The radiation is often aimed at the chest and armpit.

### **Hormone therapy**

Most male breast cancers have cells that rely on hormones to grow, called hormone sensitive. If your cancer is hormone sensitive, hormone therapy might be an option. Hormone therapy can keep cancer from coming back after surgery. If the cancer spreads to other parts of the body, hormone therapy may help slow its growth.

Hormone therapy for male breast cancer often involves the medicine tamoxifen. Other hormone therapy medicines might be an option if you can't take tamoxifen.

### **Chemotherapy**

Chemotherapy uses strong medicines to kill cancer cells. These medicines are often given through a vein. Some chemotherapy medicines are available in pill form.

Chemotherapy might be used after surgery to kill any cancer cells that might be left in the body. Chemotherapy also may be an option for treating cancer that spreads to other parts of the body.

### **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 might be used after surgery to kill any cancer cells that might be left in the body. It also might be an option if the cancer spreads to other parts of the body.

**Prevention**

For most men, there's no way to prevent male breast cancer. For those that have an increased risk of cancer, there may be ways to lower the risk.

* **If breast cancer runs in your family.** Certain DNA changes are linked to breast cancer. If these DNA changes run in your family, you might have an increased risk of breast cancer. DNA changes that increase the risk of male breast cancer include BRCA1 and BRCA2.  
  If you know that a blood relative carries DNA changes linked to breast cancer, tell your doctor or other health care professional. Together you can decide whether you should have genetic testing to see if you also carry the DNA changes.  
  If you carry a DNA change that increases your risk, you might need breast cancer screening. Usually this involves becoming familiar with the skin and tissue on your chest. Tell your health professional if you notice any changes. You also might have an annual exam of your chest.
* **If you're a transgender man.** If you haven't had gender-affirming surgery on your chest, talk with your doctor or other health care professional about breast cancer screening. In general, follow the screening guidelines for people assigned female at birth.  
  If you've had gender-affirming surgery to your chest, breast cancer is still possible, though it's rare. Often a small amount of breast tissue remains after surgery. Get to know the look and feel of the skin on your chest. Report any changes to your health care team right away.

## **Male breast cancer statistics**

Knowing the key statistics for male breast cancer is important for increasing awareness of the disease and sharing life-saving information about the importance of the early detection of male breast cancer.

Key male breast cancer statistics include:

* Male breast cancer represents about 1% of all breast cancers diagnosed in the United States.
* In 2024, about 2,800 men will be diagnosed with breast cancer in the United States.
* About 530 U.S. men will die from breast cancer in 2024.
* Male breast cancer is typically diagnosed between ages 60 to 70. The average age of men diagnosed with breast cancer in the United States is 67.
* The average lifetime risk of male breast cancer is about 1 in 726.
* Male breast cancer is 100 times less common among white men than it is among white women.
* Male breast cancer is 70 times less common for Black men than Black women.

**Male breast cancer survival rate**

When detected in its earliest, localized stages, the 5-year relative survival rate of male breast cancer is 95%, according to the American Cancer Society. This means that at the end of 5 years, 95% of men diagnosed with early-stage breast cancer will still be living.

Each stage of male breast cancer carries its own survival rate. Five-year relative survival rates at the localized, regional, and distant stages of male breast cancer are below.

### **5-year relative survival rates for male breast cancer by SEER\* stage**

| SEER stage | 5-year relative survival rate |
| --- | --- |
| Localized: Invasive cancer that has not spread outside of the breast | 95% |
| Regional: Cancer has spread outside of the breast into nearby structures or lymph nodes | 84% |
| Distant: Cancer has spread to other parts of the body, such as the bones, liver, lungs, or brain | 20% |
| All SEER stages combined | 83% |

## **Differential Diagnoses for Male Breast Cancer**

* Gynecomastia
  + The most common benign cause of male breast enlargement, characterized by proliferation of glandular tissue. Usually bilateral but can be unilateral. Distinguished clinically and by imaging.
* Pseudogynecomastia (lipomastia)
  + Fat deposition without glandular proliferation, often in overweight men.
* Invasive ductal carcinoma (IDC)
  + The most common male breast cancer (~85-90%); presents as a painless, firm, subareolar mass often with nipple retraction or skin changes.
* Ductal carcinoma in situ (DCIS)
  + Non-invasive cancer; rare in men but can present with nipple discharge or palpable mass.
* Paget’s disease of the nipple
  + Presents with eczematous changes, scaling, or ulceration of nipple/areola; often associated with underlying carcinoma.
* Lymphoma involving the breast
  + Primary or secondary involvement; may present as breast masses and axillary lymphadenopathy.
* Metastases to the breast
  + Rare; usually from prostate, lung, melanoma, or other primary cancers; often multiple bilateral masses without nipple retraction.
* Benign breast cysts or abscesses
  + Inflammatory or infectious processes causing localized swelling and tenderness.
* Dermoid cyst or sebaceous cyst
  + Benign cystic lesions presenting as palpable lumps.
* Hypogonadism-related breast changes
  + Hormonal imbalances leading to breast tissue proliferation.
* Lymphangioma
  + Rare benign vascular malformation.
* Chest wall trauma or hematoma
  + Can mimic a mass on physical exam.

**Guidelines include the following recommendations regarding follow-up:**

* Patients should be counseled about the symptoms of breast cancer recurrence, including new lumps, bone pain, chest pain, dyspnea, abdominal pain, or persistent headaches.
* Continuity of care for patients with breast cancer is recommended and should be performed by a physician experienced in the surveillance of patients with cancer and in breast examination, including the examination of irradiated breasts.
* Men with a history of breast cancer treated with lumpectomy should be offered ipsilateral annual mammography if technically feasible, regardless of genetic predisposition.
* Men with a history of breast cancer and a genetic predisposing mutation may be offered contralateral annual mammography.
* Breast magnetic resonance imaging is not routinely recommended in men with a history of breast cancer.
* Male patients with breast cancer should be offered genetic counseling and genetic testing for germline mutations

## **Doctor-Patient Conversation: Male Breast Cancer**

Doctor:  
“Thank you for coming in today. I understand this diagnosis can be overwhelming. You have been diagnosed with male breast cancer, which is rare but treatable. I want to explain what this means, discuss treatment options, and answer any questions you have.”

Patient:  
“What exactly is male breast cancer? How common is it?”

Doctor:  
“Male breast cancer is a malignant tumor arising from breast tissue in men. It’s much less common than in women, accounting for less than 1% of all breast cancers, but it behaves similarly and can be treated effectively.”

Patient:  
“What caused this? Could it be genetic?”

Doctor:  
“Some cases are linked to genetic mutations, especially in the *BRCA2* gene. We recommend genetic counseling and testing to understand if you have inherited mutations that might affect your treatment and family members.”

Patient:  
“What are the treatment options?”

Doctor:  
“Treatment usually starts with surgery to remove the tumor, often a mastectomy. Depending on the tumor type and stage, we may recommend radiation, chemotherapy, hormone therapy, or targeted therapies. Hormone therapy is important because many male breast cancers are hormone receptor positive.”

Patient:  
“What side effects should I expect from these treatments?”

Doctor:  
“Side effects vary by treatment. Surgery may cause changes in chest appearance and sensation. Radiation can cause skin irritation and fatigue. Chemotherapy may cause nausea, hair loss, and fatigue. Hormone therapy can cause hot flashes, decreased libido, and mood changes. We will provide support to manage these.”

Patient:  
“How will treatment affect my daily life?”

Doctor:  
“Some treatments require hospital visits and recovery time. You may feel tired or have other side effects, but many men continue working and doing daily activities. We’ll tailor your care to minimize impact and support your quality of life.”

Patient:  
“Should I see a specialist or get a second opinion?”

Doctor:  
“Yes, I recommend treatment at a center experienced in male breast cancer. Getting a second opinion is common and can help you feel confident about your care.”

Patient:  
“Are there support groups or resources for men like me?”

Doctor:  
“Male breast cancer is less common, so support groups specifically for men can be limited, but there are resources and helplines available. I can provide brochures and direct you to websites like the American Cancer Society and specialized male breast cancer organizations.”

Patient:  
“What should I expect after treatment? Will I need follow-up visits?”

Doctor:  
“Regular follow-up is essential to monitor for recurrence and manage any long-term effects. We’ll schedule visits with physical exams, imaging, and lab tests as needed.”

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**Insulinoma**

Insulinoma is a rare tumor in your pancreas that releases excess insulin. Insulin is the hormone that helps keep your blood sugar (glucose) at healthy levels.

Insulinoma is one of several pancreatic neuroendocrine tumors (pNETs). These are rare tumors that start in your pancreas’s endocrine cells.

About 85% to 90% of insulinomas are nonmetastatic (“indolent”). This means they don’t spread outside of your pancreas (metastasize). Metastatic (“aggressive”) insulinomas are very rare. Metastatic insulinomas are most likely to spread to your lymph nodes and/or liver.

Insulinomas release insulin. If you have insulinoma, it typically floods your body with insulin. This results in low blood sugar (hypoglycemia). When that happens, you may feel shaky. You may also feel like your heart is racing. In extreme circumstances, you may faint or have seizures.

Your symptoms should improve if you consume something that has sugar (carbohydrates). This could include apple juice, regular soda or a banana.

Experiencing low blood sugar can be scary, especially when you don’t know why it’s happening or when it’ll strike again. Keep snacks on hand and see your healthcare provider as soon as possible.

**Symptoms and Causes**

Insulinomas mainly cause low blood sugar (hypoglycemia) episodes. Symptoms of low blood sugar include:

Confusion or difficulty concentrating

Sweating

Rapid heartbeat

Anxiety or irritability

Symptoms of severe low blood sugar include:

Vision changes, like blurred vision

Slurred speech

Clumsiness or difficulty with coordination

Seizures

Loss of consciousness

Most people with insulinoma experience low blood sugar when fasting — usually in the morning when they wake up. Some people with insulinoma experience low blood sugar episodes after meals.

Persistent hypoglycemia can interfere with daily activities and cause irreversible brain damage. It can even lead to coma and death. It’s very important to see your healthcare provider if you have low blood sugar symptoms.

**What causes insulinoma?**

Insulinomas happen when the cells in your pancreas that create insulin multiply uncontrollably. Researchers aren’t sure why that happens.

But they do know that insulinoma can happen alongside multiple endocrine neoplasia type 1 (MEN1). This is an inherited condition in which multiple tumors affect different parts of your endocrine system. About 5% to 10% of insulinoma cases affect people with MEN1.

If one of your first-degree relatives (biological parents and siblings) has a MEN1 diagnosis, talk to your healthcare provider. They can recommend genetic testing that can screen for the condition. If you have MEN1, genetic testing could help detect tumors in their early phases.

**Diagnosis and Tests**

Your healthcare provider will likely suspect you have insulinoma if you have the following signs (called Whipple’s triad):

Symptoms of low blood sugar

A documented low blood sugar test result (a fingerstick blood sugar result at least less than 55 mg/dL)

Improvement of your symptoms when you eat or drink sugar (carbohydrates)

They’ll then recommend some tests to help diagnose insulinoma.

72-hour fast

Your provider may recommend fasting up to 72 hours to bring on a low blood sugar episode. This is the gold-standard test for diagnosing insulinoma. But you won’t be alone. A provider will monitor you during your fast.

Once you develop low blood sugar symptoms, you’ll get blood tests that check your:

Blood sugar level

Insulin level

Proinsulin level

C-peptide level

Beta-hydroxybutyrate level

Sulfonylurea level

After the blood draw, a provider will give you treatment for the low blood sugar.

The results of these tests can show if too much insulin (hyperinsulinemia) is causing your low blood sugar episodes.

Imaging tests

If the 72-hour fast points to insulinoma, your provider may suggest one or more of the following imaging tests:

CT scan

MRI scan

Abdominal ultrasound

Endoscopic ultrasound (EUS)

These tests can assess the tumor’s size and its location in your pancreas. If imaging tests don’t provide enough information, your provider may recommend a selective arterial calcium stimulation test. For this test, a provider measures insulin levels in your hepatic (liver) vein after stimulating arteries in various parts of your pancreas.

**Management and Treatment**

Surgery is the main treatment for nonmetastatic (indolent) insulinomas. Surgical options include:

Enucleation. Your surgeon removes the insulinoma without cutting into it. This is kind of like the way you might remove the yolk from a hard-boiled egg.

Partial pancreatectomy. As the name sounds, this surgery involves removing part of your pancreas. In this case, it’s the part where the insulinoma is.

Whipple surgery. Your surgeon removes part of your pancreas and other nearby tissues. You may need this surgery if the insulinoma is metastatic.

Each of these surgeries has different risks. Your provider will go over the risks and which surgery would be best for you.

Prevention and treatment of low blood sugar (hypoglycemia)

In the time leading up to surgery (or if surgery isn’t possible), it’s important to prevent and treat low blood sugar episodes. Your provider may recommend getting a continuous glucose monitoring (CGM) system. A CGM can help you catch low blood sugar episodes before they get too severe, especially during the night.

It’s important to remember that you shouldn’t use a CGM to diagnose insulinoma or other low blood sugar conditions. They’re for monitoring conditions after a diagnosis.

Your provider may recommend one or more of the following treatments for low blood sugar:

Dietary changes. Regular meals or snacks rich in complex carbohydrates can help prevent low blood sugar. A bedtime or late-night meal may also help.

IV glucose. If you experience frequent severe episodes of hypoglycemia, you may need to receive IV glucose.

Diazoxide. This medication can help control how much insulin your pancreas releases. It may also increase how much glucagon your liver releases. Glucagon raises your blood sugar.

Octreotide and lanreotide. These medications may help reduce the release of insulin from certain types of insulinoma tumors.

It’s important to wear medical identification that states that you experience low blood sugar. This way, someone can get you help as soon as possible if you have a severe episode. Also, tell people close to you about your low blood sugar episodes and how they can help.

**Treatment of metastatic insulinoma**

Your provider may recommend combining surgery with other treatments for metastatic (aggressive) insulinoma. Or they may use medical treatments when surgery isn’t an option. Your provider might recommend:

Peptide receptor radionuclide therapy (PRRT)

Targeted therapy

Chemotherapy

**Outlook / Prognosis**

Yes, most insulinomas can be cured with surgery. One study showed that 87% of people who had surgery for nonmetastatic insulinoma were alive 10 years after diagnosis. Your healthcare provider will consider factors like the tumor’s size and location before recommending a specific surgery.

The 10-year survival rate for metastatic insulinomas was 33%. It’s important to remember this is just an estimate. Your healthcare team will be able to give you a better idea of what to expect based on your unique situation.

**Differential diagnoses** that should also be considered when evaluating insulinomas include:

* Persistent hyperinsulinemic hypoglycemia of infancy
* Noninsulinoma pancreatogenous hypoglycemia syndrome
* Post-gastric bypass hypoglycemia
* Factitious use of insulin
* Sulfonylurea-induced hypoglycemia
* Insulin autoimmune hypoglycemia
* Non-islet-cell tumors that secrete insulin-like growth factors
* Nesidioblastosis

**STAGING**

**Tumor (T)**

* TX: Tumor cannot be assessed
* T1: Tumor limited to the pancreas, <2 cm
* T2: Tumor limited to the pancreas, 2 to 4 cm
* T3: Tumor limited to the pancreas, >4 cm; or tumor invading the duodenum or common bile duct
* T4: Tumor invasion of adjacent organs (eg, stomach, spleen, colon, adrenal gland) or the walls of large vessels (celiac axis or the superior mesenteric artery)

**Nodes (N)**

* NX: Regional lymph nodes cannot be assessed
* N0: No regional lymph node involvement
* N1: Regional lymph node involvement

**Metastasis (M)**

* M0: No distant metastasis
* M1: Distant metastasis
  + M1a: Metastasis confined to the liver
  + M1b: Metastasis in at least 1 extrahepatic site (eg, lung, ovary, non regional lymph node, peritoneum, bone)
  + M1c: Both hepatic and extrahepatic metastases

## **Epidemiology**

### United States

Insulinomas are the most common functional pancreatic endocrine tumors, comprising 55% of such cases. The incidence is 1-32 cases per million persons per year.

### International

One source from Northern Ireland reported an annual incidence of 1 case per million persons. A study from Iran found 68 cases in a time span of 20 years in a university in Tehran.A 10-year single-institution study from Spain of 49 consecutive patients who underwent laparoscopic surgery for neuroendocrine pancreatic tumors included 23 cases of insulinoma.These reports may be an underestimate.

**GENOMIC DATA**

* YY1 gene mutation (Trp372Arg / T372R): This is the most common mutation in sporadic insulinomas, found in about 30% of Asian patients and around 13-30% in Caucasian populations. This gain-of-function mutation increases YY1 transcription factor activity, upregulating genes involved in insulin secretion such as *IDH3A*, *UCP2*, *ADCY1*, and *CACNA2D2*, and is considered a driver mutation for insulinoma development.
* MEN1 gene mutations: Germline or somatic mutations in the *MEN1* tumor suppressor gene occur in approximately 10-17% of insulinomas. *MEN1* mutations are more common in hereditary syndromes like multiple endocrine neoplasia type 1 but also appear in sporadic cases. Loss of heterozygosity at 11q13 (location of *MEN1*) is frequently observed.
* ATRX and DAXX mutations: These genes, often mutated in pancreatic neuroendocrine tumors (PNETs), are less frequently mutated in insulinomas (3-8%). Alterations in *ATRX* have been linked to tumor progression and malignancy.
* K-ras mutations: Point mutations in *K-ras* codon 12 have been reported in 20-23% of insulinomas, particularly in malignant cases. These mutations may be associated with tumor progression and poor prognosis.
* Copy number variations (CNVs): Amplifications and deletions involving chromosomal regions 7p, 3p, 5q, and 13q have been identified as early events in insulinoma tumorigenesis. Specific gene CNVs involving *FOXL2*, *IRS2*, *CEBPA*, and *ATRX* may promote malignancy in β-cell populations.
* Other genetic syndromes: Up to 10% of insulinomas are linked to inherited syndromes such as MEN1, tuberous sclerosis complex, and neurofibromatosis type 1, involving germline mutations in tumor suppressor genes

## **Diagnostic Procedures and Timeline**

1. Clinical Suspicion and Whipple’s Triad Confirmation
   * Initial suspicion arises from symptoms of hypoglycemia, neuroglycopenic symptoms, and relief after glucose administration (Whipple’s triad).
2. Prolonged Fasting Test (Gold Standard Biochemical Diagnosis)
   * Patients undergo a supervised fast, usually up to 72 hours (often stopped earlier if hypoglycemia develops).
   * Blood samples are taken periodically to measure glucose, insulin, C-peptide, and proinsulin levels.
   * Diagnosis is confirmed by documented hypoglycemia (glucose <40-50 mg/dL) with inappropriately elevated insulin (>10 µU/mL), C-peptide (>2.5 ng/mL), and proinsulin levels.
   * The test usually lasts 24-48 hours but can extend to 72 hours if symptoms are delayed.
3. Imaging for Tumor Localization
   * After biochemical diagnosis, imaging is performed to locate the insulinoma:
     + Endoscopic ultrasonography (EUS): Sensitivity ~77-93%, especially good for small tumors in the pancreatic head.
     + CT scan: Sensitivity 82-94%.
     + MRI: Alternative imaging modality.
     + Selective arterial calcium stimulation test (SACST): Used if noninvasive imaging is inconclusive; involves injecting calcium into pancreatic arteries and measuring insulin response in hepatic veins, with >90% accuracy.
     + Intraoperative ultrasonography: Used during surgery to detect small or impalpable tumors, with up to 90% efficacy.
     + PET/CT with Ga-DOTATATE: Adjunct for difficult cases.
4. Surgical Treatment
   * Once localized, surgical removal is the primary treatment, with a cure rate of about 90%.
   * Surgery timing depends on patient stability and tumor localization but generally follows diagnosis promptly.
   * Intraoperative ultrasound and palpation assist in tumor identification.
5. Medical Management (if surgery is not possible or incomplete)
   * Medications like diazoxide, octreotide, or lanreotide may be used to control hypoglycemia symptom

**Doctor-patient conversation regarding insulinoma**

Doctor: "Hello, I’d like to discuss the results of your tests and what we suspect about your symptoms. Based on your episodes of low blood sugar and the symptoms you described, we are considering a condition called insulinoma. This is a rare tumor in the pancreas that produces too much insulin, which causes your blood sugar to drop unexpectedly."

Patient: "What exactly is an insulinoma? Is it dangerous?"

Doctor: "An insulinoma is usually a small, benign tumor that arises from the insulin-producing cells in your pancreas. While it can cause significant symptoms like sweating, tremors, confusion, or even fainting due to low blood sugar, it is often curable with treatment. The key is confirming the diagnosis and locating the tumor precisely."

Patient: "How do you confirm it?"

Doctor: "We perform a special test called a supervised fasting test, which can last up to 72 hours. During this time, you will be monitored closely while fasting, and we will check your blood sugar, insulin, and related hormone levels. If your blood sugar drops and your insulin remains inappropriately high, it confirms the diagnosis."

Patient: "What happens after that?"

Doctor: "Once we confirm the diagnosis biochemically, we use imaging techniques like CT scans, MRI, or endoscopic ultrasound to find the exact location of the tumor in your pancreas. Sometimes, more specialized tests are needed if the tumor is hard to locate."

Patient: "Is surgery the only option?"

Doctor: "Surgery is the primary and most effective treatment. The goal is to remove the tumor while preserving as much of your pancreas as possible. Most patients are cured after surgery. If surgery is not possible due to other health issues or if the tumor is difficult to remove, there are medications that can help control your blood sugar and reduce symptoms."

Patient: "What should I expect after surgery?"

Doctor: "After surgery, we will monitor your blood sugar closely to ensure it stabilizes. You’ll have follow-up visits to check for any recurrence, but the prognosis is generally very good, especially if the tumor is benign and completely removed."

Patient: "Are there any risks or complications?"

Doctor: "Like any surgery, there are risks such as infection or bleeding, but these are relatively low with modern techniques. We also aim to minimize the impact on your pancreas to preserve its function."

Patient: "Thank you, that helps me understand a lot better."

Doctor: "You’re welcome. We will support you throughout this process and make sure you get the best care possible. If you have any questions at any time, please don’t hesitate to ask."

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## 

## GASTRINOMA

## **Alternative names for gastrinoma**

Zollinger-Ellison syndrome; Z-E syndrome; ZES

Gastrinomas are neuroendocrine tumours that produce large quantities of the hormone gastrin, which stimulates the production of excess gastric acid from the stomach. Most of these tumours are found either in the duodenum (first part of the small intestine) or the pancreas (gastric triangle). Very rarely they have been found in the liver, stomach, bile duct, heart and lung.

## **What causes gastrinomas?**

* G cells in the stomach, pancreas and small intestine stimulate the parietal cells in the stomach.
* This produces the hormone gastrin. Usually, gastrin increases stomach acid to help with the digestion of food.
* Gastrinomas are overgrowth of G cells, which lead to production of excessive amounts of gastrin The increased acid production causes erosions or ulcers in the stomach and small intestine.
* Gastrinomas often develop spontaneously (sporadic tumours) However, in approximately 20-30% of patients these tumours may develop as part of a syndrome called multiple endocrine neoplasia type 1 (MEN1).

## **Signs and symptoms of gastrinomas**

The signs and symptoms of gastrinomas are related to increased gastric acid production as shown in the figure below.

On average symptoms may be present up to five years before a definitive diagnosis of gastrinoma is established.

Ulcers of the stomach and small intestine are not uncommon in the general population, however only a very small number of these ulcers occur due to the presence of a gastrinoma, (approximately 0.1% (1 in 1000) of patients who have ulcers in these locations). Some symptoms may increase suspicion of a Gastrinoma.

The diagnosis of gastrinoma may be suspected in patients with stomach or small intestinal ulcers if they:

* Are resistant to treatment
* Have recurrent ulcers
* Have associated complications such as intestinal perforation and bleeding
* Have other features of MEN1 syndrome e.g. elevated calcium levels
* Have a family history of MEN1 syndrome

## **Zollinger Ellison Syndrome**

Zollinger-Ellison syndrome is a rare syndrome caused by a gastrinoma, which is characterised by severe, recurrent, and multiple peptic ulcers in the first part of the small intestine (such as the duodenum) or pancreas.

Gastrinomas are rare; they have an incidence of 0.5–3 new cases per million of the population per year. They are slightly more common in men compared with women (1.5:1).

Most sporadic gastrinomas are diagnosed in people aged between 50 to 60 years.   
Gastrinoma tumours arising as part of the genetic condition multiple endocrine neoplasia type 1 are usually diagnosed at a younger age (20’s to 30’s).

## **DIAGNOSIS**

Gastrin measurement:

The diagnosis of a gastrinoma is based on confirming that there is a high level of gastrin in the blood when the person is fasting. However, proton pump inhibitors (PPI) such as omeprazole or lansoprazole, a treatment for indigestion can interfere with the results. This can cause diagnostic difficulties and PPI medication is often stopped temporarily before the gastrin blood test is taken, when it is safe to do so.

Secretin test:

In cases where the measurement of gastrin while fasting is inconclusive a secretin test may be carried out. Secretin is a hormone produced by the small intestine, which stimulates pancreatic and small intestinal secretions, in this case it will cause a gastrinoma to release more gastrin. The test requires an injection of secretin into the blood, if this causes a rise in gastrin levels, along with evidence of increased acid production in the stomach – measured during an endoscopy, this would suggest an underlying diagnosis of gastrinoma. This test is usually carried out in an outpatient setting.

Imaging studies:

To locate the gastrinoma, certain scans such as a computerised tomography (CT) or magnetic resonance imaging (MRI), may be performed. In addition to identifying the location of the gastrinoma the scans may also determine if there has been any spread of the tumour cells to other organs. However, often gastrinoma is small and may not be seen on CT or MRI.

Specialised scans include somatostatin receptor scintigraphy (SRS/OctreoScan) and 68 gallium-labelled somatostatin tracer PET/CT (positron emission tomography/computerised tomography) scan which are specific for secretion by neuroendocrine tumours like gastrinomas.

Tissue Biopsy:

Biopsy of suspicious areas can be done using endoscopic ultrasound; this is where a camera is passed down through the oesophagus, stomach and through the first part of the small intestine, it is very useful for assessing the pancreas for the presence of small tumours.

A biopsy is where a small sample of the tumour is taken to be looked at under a microscope to confirm diagnosis.

## **Are Gastrinomas cancerous?**

Some gastrinomas are benign however majority are malignant which means that they may spread to nearby organs. Gastrinomas associated with MEN 1 are usually more aggressive than sporadic forms.

## **How is a Gastrinoma Treated?**

Treatment decisions will be based on the size, location, spread of the tumour and whether it has developed as part of a MEN1 syndrome or not.

Treatment decisions are often made at multidisciplinary team (MDT) meetings (a meeting that takes place between different healthcare professionals to discuss a patient’s care) which may be a neuroendocrine MDT at a specialist centre and varies as below:

Management of symptoms:

High doses of acid-blocking agents such as proton pump inhibitors or H2 receptor antagonists may be needed on a long-term basis to reduce gastric acid secretion, which relieves the symptoms and promotes the healing of ulcers in the small intestine and stomach.

Surgical Resection:

In cases where the gastrinoma is localised to the pancreas or small intestine without any evidence of spread to other organs, surgical removal of the tumour can cure the disease.

Management of tumour progression:

In patients where the gastrinoma has spread to the liver (called metastasis) and surgical treatment will not achieve a cure and somatostatin analogues such as octreotide/lanreotide may be used for stabilisation of the disease.

In some cases where the tumour spread is aggressive then alternative treatments may be used and these include:

* Chemotherapy
* Tyrosine kinase inhibitors or mTor inhibitors
* Peptide targeted radionuclide therapy (PRRT)
* Trans-arterial embolisation/chemoembolization.

## **Side-effects to the treatment**

* There are general risks associated with surgery such as possible loss of blood, infection and pain following surgery.
* Long-term use of proton pump inhibitors (PPI’s) has been linked with development of vitamin B12 deficiency and low magnesium levels; these can be monitored with blood tests. The use of PPI’s has also been linked to an increased risk of bone fractures.
* Somatostatin analogue therapy is associated with side-effects such as nausea, diarrhoea, worsening of diabetes control and gallstone formation.
* Chemotherapy is associated with side-effects such as bone marrow suppression, loss of hair (alopecia) and gastrointestinal disturbance although patients should discuss any concerns about these possible side-effects with their doctor or specialist as it will depend on the specific treatments used.
* PRRT can affect bone marrow and kidneys.
* Trans arterial embolisation can cause some discomfort and damage surrounding healthy liver tissue.

## **Longer-term implications of a gastrinoma**

* In cases where the tumour has not spread to any adjacent organs and may successfully be removed by surgery, patients should go on to lead full and active lives. They will be followed up as sometimes there can be long-term issues with pancreatic hormones and enzymes not being produced in usual amounts, this can affect food absorption and occasionally the development of diabetes.
* Patients treated with surgery will need to attend regular hospital checks to assess for recurrence of the tumour using blood tests or radiological investigations
* Gastrinoma, if left untreated, can lead to ulcers, perforation and bleeding from the stomach and small intestine.
* These neuroendocrine tumours are usually slow growing and proton pump inhibitors are highly effective in controlling the symptoms. However, when they spread to other organs such as the liver and a cure cannot be achieved then this can limit life expectancy.

### **Can treatment cure Zoller-Ellison syndrome?**

Surgery to remove cancerous gastrinomas may cure the condition. But a cure depends on removing all cancerous cells in your body. If surgery is successful, you’ll need to take medication to manage gastric acid for the rest of your life.

## **Outlook / Prognosis**

Your prognosis, or what you can expect after treatment, depends on the tumor type. Noncancerous gastrinoma tumors aren’t life-threatening. You may need ongoing treatment to manage stomach acid levels.

The situation changes if you have cancerous tumors. In that case, you may need surgery and follow-up cancer treatment.

#### **Survival rates for Zollinger-Ellison syndrome**

Zollinger-Ellison survival rates vary. Experts estimate more than 90% of people will live between five and 10 years after surgery removes all gastrinoma tumors. The five-year survival rate estimate drops to 43% in cases where surgery doesn’t remove all tumors. It’s important to remember that cancer survival rates are estimates. If you have ZES, ask your healthcare provider what you can expect.

## **Living With**

That depends on your situation. Most people will always need medication to reduce gastric acid. Zollinger-Ellison syndrome happens because you have gastrinoma tumors. Most of these tumors are cancerous. If you have cancerous tumors, you’ll need follow-up care to confirm the tumors haven’t come back.

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

You should contact your provider if Zollinger-Ellison symptoms get worse after treatment or come back.

**Differential diagnoses (DDX) for gastrinoma**

* Peptic Ulcer Disease (PUD) (due to H. pylori infection or NSAIDs)
* Gastroesophageal Reflux Disease (GERD)
* Antral G-cell hyperplasia / Gastric antrum syndrome
* Atrophic gastritis / Pernicious anemia (causing achlorhydria with compensatory hypergastrinemia)
* Gastric outlet obstruction (secondary hypergastrinemia)
* Multiple endocrine neoplasia type 1 (MEN1) (associated with gastrinoma and other endocrine tumors)
* Non-gastrinoma causes of hypergastrinemia:
  + Proton pump inhibitor (PPI) use
  + Renal insufficiency
  + Massive intestinal resection
  + Chronic atrophic gastritis
  + Helicobacter pylori infection
* Other hormone-secreting tumors causing diarrhea or abdominal symptoms:
  + VIPoma
  + Carcinoid tumors
* Inflammatory bowel disease (IBD)
* Irritable bowel syndrome (IBS)
* Small bowel bacterial overgrowth
* Chronic pancreatitis
* Mesenteric ischemia
* Lymphoma or other small bowel enteropathies (rare)
* Autonomic neuropathy
* Factitious diarrhea

**EPIDEMIOLOGY**

Gastrinomas are rare neuroendocrine tumors with an estimated annual incidence of 0.5 to 2 cases per million individuals. Approximately 80% of gastrinomas occur sporadically and are typically diagnosed in patients approximately 50 years old, with a slight male predominance. The remaining cases are associated with MEN1 and present earlier in life, often between the ages of 20 and 30.

Gastrinomas have been reported in various anatomic sites, primarily known as the “gastrinoma triangle,” which is an anatomic area in the abdomen with boundaries formed superiorly by the confluence of the cystic and common bile ducts, inferiorly by the second and third portions of the duodenum, and medially by the neck of the pancreas. Approximately 70% to 90% of gastrinomas arise in the duodenum, while 10% to 30% occur in the pancreas. Duodenal tumors, though, are generally smaller in size and more likely to metastasize to regional lymph nodes compared to pancreatic gastrinomas. Unfortunately, despite their indolent growth, the majority of gastrinomas are malignant, and approximately 60% have metastasized at the time of diagnosis.

**procedures for gastrinoma typically follow this timeline:**

## 1. Initial Evaluation and Biochemical Testing

* Medical history and physical exam: Assess symptoms like recurrent peptic ulcers, diarrhea, and acid reflux resistant to treatment.
* Fasting serum gastrin level: Elevated gastrin (>1000 pg/mL) with low gastric pH (<2) is highly suggestive of gastrinoma.
* Secretin stimulation test: Used if gastrin levels are moderately elevated (<1000 pg/mL). A paradoxical increase in gastrin after secretin injection supports the diagnosis.
* Additional blood tests: Chromogranin A (often elevated), Helicobacter pylori testing, and exclusion of other causes of hypergastrinemia (e.g., PPI use, renal failure).

## 2. Tumor Localization

* Imaging studies:
  + Contrast-enhanced CT scan: Detects tumors >1 cm, pancreatic head tumors, and liver metastases.
  + MRI: High specificity for small pancreatic tumors and liver metastases.
  + Somatostatin receptor scintigraphy (Octreoscan) or 68Ga-DOTATATE PET/CT: High sensitivity and specificity for detecting gastrinomas and metastases, especially small lesions.
  + Endoscopic ultrasound (EUS): Particularly useful for small pancreatic tumors; allows fine-needle aspiration biopsy for histological confirmation.
* Selective arterial secretin injection test: May be used if imaging is inconclusive.

## 3. Surgical Exploration and Treatment

* Surgery:
  + Indicated for localized tumors; goal is complete tumor resection.
  + Intraoperative palpation, intraoperative ultrasound, and endoscopy are used to identify small or occult tumors, especially in the duodenum.
  + Duodenotomy and full-thickness excision of suspicious lesions may be necessary if preoperative imaging is negative.
* Surgery is usually planned shortly after localization studies confirm tumor presence.

## 4. Postoperative Follow-up and Medical Management

* Monitoring: Regular follow-up with gastrin levels and imaging to detect recurrence or metastases.
* Medical therapy: Proton pump inhibitors to control acid hypersecretion; somatostatin analogs may be used if surgery is not feasible or for metastatic disease.

## N**M Staging Overview for Gastrinoma**

| **Stage** | **Description** |
| --- | --- |
| Stage I | Small, localized tumor confined to the pancreas or duodenum (T1), no lymph node (N0) or distant metastasis (M0). Tumor ≤ 2 cm, limited to mucosa/submucosa or ≤1 cm in duodenal NETs. |
| Stage II | Larger tumor (T2 or T3), still no lymph node or distant spread (N0, M0). Tumor invades muscularis propria or >2 cm but no nodal involvement. |
| Stage III | Locally advanced tumor invading adjacent structures (T4) or any tumor with regional lymph node metastasis (N1), no distant metastasis (M0). |
| Stage IV | Presence of distant metastases (M1), commonly to the liver or bones. |

## 

## Tumor size and invasion (T):

## T1: Tumor ≤2 cm, limited to pancreas or mucosa/submucosa in duodenum.

## T2: Tumor >2 cm but confined to pancreas/duodenum.

## T3: Tumor invades beyond the pancreas into surrounding tissues.

## T4: Tumor invades adjacent organs or visceral peritoneum.

## Nodal status (N):

## N0: No regional lymph node metastasis.

## N1: Regional lymph node metastasis present.

## Metastasis (M):

## M0: No distant metastasis.

## M1: Distant metastasis present.

## Grading

## Gastrinomas are generally well-differentiated NETs and graded based on mitotic count and Ki-67 proliferation index:

## Grade 1 (low grade): Slow-growing tumors.

## Grade 2 (intermediate grade).

## Grade 3 (high grade): Rare in gastrinomas, more aggressive.

## **Doctor-patient conversation about gastrinoma**

## Doctor: "Based on your symptoms and test results, we suspect you have a condition called a gastrinoma. This is a rare tumor that produces excess gastrin, a hormone that causes your stomach to make too much acid. This excess acid can lead to severe and recurrent ulcers, and sometimes diarrhea."

## 

## Patient: "Is this serious? What causes it?"

## 

## Doctor: "Gastrinomas can be serious because the excess acid can damage your digestive tract and cause complications. Most gastrinomas are tumors in the pancreas or the duodenum. Some occur sporadically, while others are part of a genetic syndrome called multiple endocrine neoplasia type 1, or MEN1."

## 

## Patient: "How do you confirm the diagnosis?"

## 

## Doctor: "We measure your fasting gastrin levels and check the acidity in your stomach. If the gastrin is very high and your stomach acid is also high, that strongly suggests a gastrinoma. Sometimes, we do a special test called the secretin stimulation test to confirm. After that, we use imaging like CT scans, MRI, or specialized scans to find the tumor."

## 

## Patient: "What treatment options are there?"

## 

## Doctor: "The main treatment is surgery to remove the tumor if it hasn’t spread. Surgery offers the best chance for cure, especially if the tumor is localized. In the meantime, and if surgery isn’t possible, we use medications called proton pump inhibitors to reduce stomach acid and protect your digestive tract. For advanced cases, other treatments like chemotherapy or targeted therapies may be considered."

## 

## Patient: "What are the risks of surgery?"

## 

## Doctor: "Surgery is generally safe but can have risks like any operation, including infection or bleeding. Also, some gastrinomas are small and multiple, especially in MEN1 patients, which can make surgery more complex. We will carefully plan your surgery with a specialized team to minimize risks."

## 

## Patient: "Will I need long-term follow-up?"

## 

## Doctor: "Yes, gastrinoma patients need long-term follow-up because the tumor can recur or spread. We will regularly monitor your gastrin levels and do imaging studies to catch any changes early."

## 

## Patient: "Thank you, that helps me understand what to expect."

## 

## Doctor: "You’re welcome. We will support you throughout your treatment and follow-up. Please feel free to ask any questions at any time."

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### **Glucagonoma**

A glucagonoma is a rare pancreatic tumor that releases glucagon, a hormone. It’s a type of pancreatic neuroendocrine tumor (islet cell tumor).

Glucagon is a natural hormone your body makes that helps manage blood glucose (sugar) levels. Specific cells in your pancreas called alpha cells make glucagon. Glucagon triggers your liver to release stored glucose (glycogen) to raise your blood sugar. Your body normally releases glucagon in response to a drop in blood sugar, prolonged fasting, exercise and protein-rich meals.

A glucagonoma can release excess glucagon. This leads to glucagonoma syndrome, which involves several symptoms and complications, like a painful skin rash and diabetes.

Most glucagonomas begin in the tail or body of your pancreas.

#### **Is glucagonoma a cancer?**

A glucagonoma is usually cancerous. About 50% of people have metastasis (the cancer has spread) when they receive a diagnosis. It most commonly spreads to your liver.

Glucagonoma is very rare. There’s less than 1 new case per 1 million people a year. It mostly affects people who are 50 to 70 years old.

## **Symptoms and Causes**

Glucagonomas tend to grow slowly. If you have one that isn’t releasing enough excess glucagon to cause issues for your body, you likely won’t have any symptoms.

If a glucagonoma releases excess glucagon that your body can’t keep up with, it triggers glucagonoma syndrome. This condition has noticeable symptoms. If you develop these symptoms, it’s important to see a healthcare provider as soon as possible.

#### **Glucagonoma skin rash**

The most common symptom of glucagonoma syndrome is a widespread skin rash called necrolytic migratory erythema (NME). It affects about 90% of people with the syndrome.

The rash can be on any part of your body, but it most often starts in your genital and anal regions, buttocks and lower legs. Other features of NME include:

* It may come and go and move around your body.
* It’s often itchy and painful in the beginning.
* It starts as a ring-shaped reddish area that blisters and crusts over. As the area heals, it may leave behind a brownish mark.
* It can cause a sore smooth tongue (glossitis), a sore mouth, cracked dry lips and angular cheilitis.
* It can cause inflamed eyelids (blepharitis), hair loss and issues with your nails.

#### **Diabetes symptoms**

The syndrome can lead to high blood sugar (hyperglycemia), which causes diabetes. Symptoms of diabetes include:

* Unexplained weight loss.
* Excessive thirst (polydipsia).
* Frequent urination (polyuria), especially overnight.
* Increased appetite or intense hunger (polyphagia).

#### **Other symptoms of glucagonoma syndrome**

Other symptoms of glucagonoma syndrome include:

* Chronic diarrhea.
* Anemia, which can cause fatigue, dizziness and other symptoms.
* Blood clots, especially deep vein thrombosis.

It can cause neurological and psychiatric symptoms, including:

* Depression.
* Dementia.
* Agitation.
* Hyperreflexia.
* Ataxia.
* Psychosis.
* Paranoid delusions.

### **What causes glucagonoma?**

In most cases, healthcare providers don’t know the cause of glucagonoma. In about 10% of cases, the tumor is linked to an inherited condition called multiple endocrine neoplasia type (MEN) type 1.

However, even among people with MEN type 1, only a very small percentage will develop a glucagonoma.

## **Diagnosis and Tests**

If you have necrolytic migratory erythema (NME), a healthcare provider will likely suspect glucagonoma and order tests. These tests may include:

* Fasting blood sugar test: An elevated level helps point to glucagonoma and can help confirm diabetes related to glucagonoma.
* Fasting glucagon blood test: With glucagonoma, glucagon levels are abnormally elevated — usually greater than 500 picograms per milliliter (pg/mL). Normal fasting blood glucagon levels are less than 150 pg/mL.
* Amino acid blood test: Glucagonoma usually causes hypoaminoacidemia (low levels of amino acids).
* Complete blood count: This test checks for anemia, which can happen with glucagonoma.

Imaging tests can confirm the presence of a tumor. They may include:

* CT scan.
* MRI scan.
* Endoscopic ultrasound.

## **Management and Treatment**

The treatment for glucagonoma largely depends on whether the tumor is localized (just in your pancreas) or has metastasized (spread to other parts of your body).

Initial treatment for glucagonoma involves managing the symptoms and complications related to excess glucagon. Treatments include:

* Medications to manage glucagon excess: Octreotide and lanreotide injections can help reverse the effects of glucagon excess, as well as prevent the release of glucagon. These medications may also slow down the tumor’s growth. They can also help treat NME, diabetes, diarrhea and neurological symptoms.
* Management of diabetes: You may need oral diabetes medications or insulin injections to keep your blood sugar levels in a healthy range.
* Nutritional support: This may include total parenteral nutrition (TPN) and supplementation of amino acids and zinc to reverse the effects of malnutrition.
* Management of NME: Antibiotics and corticosteroids may help improve NME.
* Anticoagulant therapy: Blood-thinning medication (like heparin) can help prevent deep vein thrombosis.

#### **Treatment for localized glucagonoma**

If the tumor is only in your pancreas, surgery is the main treatment. If your surgeon can completely remove the tumor, then it’s usually cured. Once the glucagonoma is gone, your glucagon levels should return to normal. Your symptoms should also go away.

#### **Treatment for metastasized glucagonoma**

When possible, your healthcare provider will recommend surgery to remove tumors. This may include tumors in your pancreas, nearby lymph nodes and liver.

If your surgeon can’t remove any or all of the tumor(s), your healthcare team will likely recommend one or more of the following:

* Chemotherapy: This treatment aims to destroy cancer cells and prevent them from multiplying.
* Radiofrequency ablation: This treatment uses heat from radio waves to kill tumor cells.
* Cryosurgical ablation: This treatment uses extremely cold chemicals, like liquid nitrogen, to destroy cancerous cells.
* Chemoembolization: This treatment blocks a tumor’s blood supply.

## **Outlook / Prognosis**

The prognosis (outlook) for people with glucagonoma depends on several factors, including:

* Your age and overall health.
* The tumor size.
* If the tumor has spread or not.

The outlook is usually good if the tumor is contained within your pancreas. Surgery to remove the tumor typically cures these cases. But this represents only about 20% of glucagonoma cases.

Glucagonomas are very rare, so there’s not much data that can predict survival rates and outcomes for metastasis. Your healthcare team will be able to provide more information based on your unique situation.

## **Prevention**

As scientists don’t know the cause of most cases of glucagonoma, there’s nothing you can do to prevent it.

If one of your first-degree relatives (biological parents and siblings) has a multiple endocrine neoplasia (MEN) diagnosis, talk to your healthcare provider about genetic testing that can screen for the condition. If you do have MEN, genetic testing could help detect tumors in their early phases.

**DIFFERENTIAL DIAGNOSIS**

Skin Rash Differential Diagnoses (Necrolytic Migratory Erythema-like lesions)

* + Acrodermatitis enteropathica (zinc deficiency)
  + Pellagra (niacin deficiency)
  + Psoriasis (especially pustular psoriasis)
  + Chronic eczema / atopic dermatitis
  + Pemphigus foliaceus (autoimmune blistering disease)
  + Other nutritional deficiencies (essential fatty acids, amino acids)
  + Myelodysplastic syndromes
  + Celiac disease, inflammatory bowel disease (IBD)
  + Hepatitis B and other liver diseases
* Causes of Hyperglycemia / Diabetes-like Symptoms
  + Type 1 and Type 2 diabetes mellitus
  + Cushing syndrome (glucocorticoid excess)
  + Renal failure (impaired glucose metabolism)
  + Severe stress or critical illness
  + Acute pancreatitis
  + Prolonged fasting or starvation states
* Other Conditions with Similar Systemic Features
  + Multiple endocrine neoplasia type 1 (MEN1) (may be associated with glucagonoma)
  + Familial hyperglucagonemia (non-tumoral glucagon excess)
  + Autoimmune and hereditary chronic pancreatitis
  + Mahvash disease (glucagon receptor mutation causing alpha-cell hyperplasia)

**EPIDEMIOLOGY**

Glucagonomas are exceedingly rare neoplasms, with an estimated annual incidence ranging from 0.01 to 0.1 new cases per 100,000 individuals. These tumors most commonly present in individuals between the fifth and sixth decades of life, with no significant difference in incidence between males and females

**Genomic data on glucagonoma**

* DAXX gene biallelic inactivation: Sporadic glucagonomas often show biallelic inactivation of the *DAXX* gene, which, together with *ATRX*, regulates chromatin remodeling at telomeric and pericentromeric regions. These alterations affect tumor biology and chromatin structure.
* GCGR gene mutations: Approximately 50% of cases with glucagon cell hyperplasia and neoplasia harbor germline mutations in the *GCGR* gene (glucagon receptor gene) located on chromosome 17q25.3. These mutations can lead to dysfunctional glucagon receptor signaling, contributing to alpha-cell proliferation and tumor development.
* MEN1 syndrome association: About 13-17% of glucagonomas occur in the context of multiple endocrine neoplasia type 1 (MEN1), a hereditary tumor syndrome caused by mutations in the *MEN1* tumor suppressor gene. Glucagonomas in MEN1 patients may also show mutations in the *FOXA2* gene, important for islet cell development.
* Other inherited tumor syndromes: Though rare, glucagonomas may be linked to genetic syndromes such as neurofibromatosis type 1 (NF1) and tuberous sclerosis complex (TSC), which involve germline mutations in tumor suppressor genes.
* Mahvash disease: A rare disorder caused by inactivating mutations in the *GCGR* gene, leading to hyperglucagonemia and alpha-cell hyperplasia without overt glucagonoma syndrome.
* Additional mutations: Some glucagonoma cases show mutations in *ATRX* and other chromatin remodeling genes, similar to other pancreatic neuroendocrine tumors.

**procedures and timeline**

## 1. Clinical Suspicion and Initial Evaluation

* Patients usually present with symptoms such as necrotic migratory erythema (NME) rash, weight loss, diabetes or glucose intolerance, diarrhea, and cachexia.
* Initial clinical evaluation includes detailed history and physical exam focusing on these symptoms.

## 2. Laboratory Testing

* Fasting serum glucagon level: Markedly elevated glucagon confirms suspicion.
* Serum glucose: Usually elevated due to glucagon-induced hyperglycemia.
* Chromogranin A: Used as a tumor marker and for monitoring disease activity.
* Other labs may include amino acid levels and nutritional markers.

## 3. Imaging for Tumor Localization

* Multiphasic contrast-enhanced CT scan or MRI: First-line imaging to localize the pancreatic tumor and assess for metastases, especially in liver and lymph nodes.
* If CT/MRI is inconclusive, proceed to:
* Somatostatin receptor scintigraphy (OctreoScan) or 68Ga-DOTATATE PET/CT: Highly sensitive for detecting primary and metastatic lesions.
* Endoscopic ultrasound (EUS): Useful for small tumors and allows biopsy.

## 4. Histological Confirmation

* Biopsy (often via EUS) confirms diagnosis with immunohistochemical staining positive for glucagon, chromogranin A, and synaptophysin.
* Ki-67 index and tumor grading guide prognosis.

## 5. Treatment Planning

* Surgical resection is the mainstay if the tumor is localized and operable. This may include distal pancreatectomy and splenectomy if located in the body or tail.
* For metastatic disease, surgery may be palliative, combined with other therapies.

## 6. Medical Management

* Control of hyperglycemia with insulin or oral agents.
* Nutritional support and management of rash and other symptoms.
* Somatostatin analogs (octreotide, lanreotide) to reduce hormone secretion and tumor growth.

## 7. Post-treatment Monitoring

* Regular follow-up with serum glucagon and chromogranin A levels.
* Periodic imaging to detect recurrence or progression.

**Doctor-patient conversation about glucagonoma**,

Doctor: "Based on your symptoms and test results, we believe you have a condition called glucagonoma. This is a rare type of tumor that arises from certain cells in your pancreas and produces too much of a hormone called glucagon."

Patient: "What does glucagon do, and how does this tumor affect me?"

Doctor: "Glucagon normally helps regulate your blood sugar by raising it when it gets too low. But when a tumor like this makes too much glucagon, it can cause high blood sugar, weight loss, and a distinctive skin rash called necrolytic migratory erythema, which you have. It can also cause diarrhea and other symptoms."

Patient: "Is it dangerous? What are the next steps?"

Doctor: "Glucagonomas are often slow-growing but can be malignant and spread to other organs like the liver. Early diagnosis and treatment are important. We confirmed your diagnosis with blood tests showing very high glucagon levels and imaging that found the tumor in your pancreas."

Patient: "How do you treat it?"

Doctor: "If the tumor is localized and operable, surgery to remove it is the best chance for a cure. Because these tumors often cause symptoms from hormone excess, we also use medications called somatostatin analogues, like octreotide, to reduce glucagon secretion and control symptoms like the rash and diarrhea."

Patient: "What if the tumor has spread?"

Doctor: "If there is spread to the liver or lymph nodes, surgery may still be helpful to reduce tumor burden, but additional treatments like chemotherapy, targeted therapies, or procedures to control liver metastases may be needed. We also manage symptoms carefully to maintain your quality of life."

Patient: "What should I expect after surgery?"

Doctor: "After surgery, we will monitor your hormone levels and symptoms regularly. The rash and other symptoms usually improve quickly. Long-term follow-up is important because these tumors can recur or progress slowly over time."

Patient: "Are there any side effects or risks I should know about?"

Doctor: "As with any surgery, there are risks like infection or bleeding, but we take every precaution. The medications can have side effects like gastrointestinal discomfort, but they are generally well tolerated. We will support you throughout your treatment."

Patient: "Thank you. It helps to understand what’s going on and what to expect."

Doctor: "You’re welcome. We’ll work together to manage this and keep you as comfortable and healthy as possible. Please feel free to ask questions anytime."

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### **VIPoma tumor**

A VIPoma (vasoactive intestinal peptide secreting) tumor is a rare type of pancreatic neuroendocrine tumor. It develops in your pancreas’s endocrine cells. The tumors cause chronic (long-term) watery diarrhea. Healthcare providers may refer to this condition as Verner-Morrison syndrome.

VIPomas are very rare. Experts estimate 1 in 10 million people in the U.S. will develop this condition. It can be challenging to live with a very rare disease that disrupts your daily life. But healthcare providers have treatments that may cure VIPoma or help ease its symptoms.

## **Symptoms and Causes**

The most significant symptom is severe watery diarrhea that happens even when you’re not eating (fasting) or doesn’t get better within a few days. Other symptoms are:

* Belly cramps
* Fatigue
* Flushing, when your face and chest suddenly turn red for no reason
* Weak muscles

### **What causes VIPoma?**

Experts don’t know the exact cause. They do know VIPoma symptoms happen when the tumor releases unusually large amounts of a certain hormone. This is the vasoactive intestinal peptide (VIP) hormone. It supports your digestion. It manages the release of water, salts, enzymes and gastric acid in your digestive system. It also relaxes certain muscles in your digestive tract. In VIPoma, large amounts of the VIP hormone trigger symptoms like severe watery diarrhea and belly cramps.

### **Complications of VIPoma**

VIPoma triggers floods of watery diarrhea. Some people produce 1 to 3 quarts of watery poop every day. Over time, people develop dehydration and hypokalemia (low levels of potassium). Those conditions may lead to serious medical issues like:

* Arrhythmia
* Hypovolemic shock
* Myopathy
* Tetany

## **Diagnosis and Tests**

A healthcare provider will do a physical examination. They’ll ask about your symptoms, like watery diarrhea and belly cramps that last for more than a few days. They may do a stool test to rule out other common diseases that cause diarrhea. Other tests may include:

* Blood tests, including tests measuring VIP hormone levels
* Imaging tests like a computed tomography scan or magnetic resonance imaging (MRI) test

## **Management and Treatment**

Treatment may be a combination of medication and surgery. A healthcare provider may prescribe:

* IV fluids to replace fluids and minerals lost because you had ongoing diarrhea
* Medication like octreotide (Sandostatin LAR®), which controls diarrhea

Once your symptoms are under control, your provider may recommend the following:

* Chemotherapy
* Targeted therapy

A distal pancreatectomy removes the body and tail of your pancreas. It’s an option in cases when a tumor hasn’t spread (metastasized) to another area of your body.

## **Outlook / Prognosis**

Surgery may cure VIPoma. Medication may reduce VIPoma symptoms. But everyone’s situation is different. What you can expect may be very different from what other people with VIPoma may experience. Your surgeon and healthcare team know you and your situation. They’re your best resources for information.

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

If you’re receiving treatment for VIPoma, contact your healthcare provider if your symptoms don’t go away or get worse. Go to the emergency room if you have:

* Severe belly pain
* Watery diarrhea that lasts for several days
* Dehydration symptoms like feeling weak or lightheaded or you have dark-colored pee

**EPIDEMIOLOGY**

VIPomas are rare tumors that are detected in 1 in 1,000,000 people per year. In adults, they are most commonly diagnosed between the ages of 30 and 50 and are intrapancreatic in over 95% of cases. A small proportion of tumors secreting VIP have been reported as colorectal cancer, lung cancer, pheochromocytoma, neurofibroma, and ganglioneuroblastoma. Most VIPomas present as isolated, functioning neuroendocrine tumors predominantly located in the pancreatic body and tail. Approximately 5% of cases are associated with multiple endocrine neoplasia type 1 syndrome. Notably, over 50% of VIPomas exhibit metastatic disease at the time of diagnosis.

In children, VIPomas are typically diagnosed between the ages of 2 to 4. Most of these tumors in the pediatric population are either ganglioneuromas or ganglioneuroblastomas, arising from the neural crest tissue of the sympathetic ganglia in the mediastinum or retroperitoneum. They may also arise from the adrenal medulla

## **Diagnostic Considerations**

In addition to the conditions listed in the differential diagnosis, other problems to be considered include the following:

* Enteric anendocrinosis
* Enteric dysendocrinosis
* All conditions with diarrhea
* Ganglioneuroblastoma (similar symptoms; mainly found in children)
* Infectious diseases of the intestines
* Laxative abuse
* Villous adenoma of the rectum

## 

## **Differential Diagnoses**

* Emergent Treatment of Gastroenteritis
* Gastrinoma
* Intestinal Carcinoid Tumor
* Medullary Thyroid Carcinoma
* Neuroblastoma Imaging
* Pancreatic Cancer
* Pediatric Multiple Endocrine Neoplasia
* Somatostatinomas
* Celiac Disease (Sprue) Imaging
* Tropical Sprue
* Villous Adenoma
* Multiple Endocrine Neoplasia Type 1 (MEN1)
* Zollinger-Ellison Syndrome

**procedures and timeline for VIPoma**

## 1. Initial Clinical Evaluation

* History and physical exam: Focus on symptoms such as profuse watery diarrhea (often >1-3 liters/day), muscle cramps, weakness, dehydration, and weight loss.
* Rule out common causes of diarrhea with stool tests and clinical assessment.

## 2. Laboratory Testing

* Serum VIP level: Elevated levels (>200 pg/mL) confirm diagnosis.
* Electrolytes: Hypokalemia and metabolic acidosis are common and require correction.
* Other labs: Serum bicarbonate, calcium, glucose, liver function tests, and chromogranin A may be measured.

## 3. Imaging for Tumor Localization

* Contrast-enhanced CT or MRI of the abdomen: To locate the pancreatic tumor and assess for metastases.
* Somatostatin receptor imaging (Octreoscan or 68Ga-DOTATATE PET/CT): Highly sensitive for detecting primary and metastatic lesions.
* Endoscopic ultrasound (EUS): Useful for detecting small pancreatic tumors and obtaining biopsy samples.

## 4. Symptomatic and Medical Management

* Immediate fluid and electrolyte replacement: Intravenous fluids, potassium, and bicarbonate to correct dehydration, hypokalemia, and acidosis.
* Somatostatin analogues (octreotide or lanreotide): To reduce VIP secretion and control diarrhea; doses may need to be high initially.
* Additional medications: Glucocorticoids may be used if somatostatin analogues are insufficient.

## 5. Surgical Treatment

* Surgical resection: If the tumor is localized and operable, surgery offers the best chance for cure (about 50% cure rate).
* Surgery may be delayed until symptoms and electrolyte imbalances are stabilized.

## 6. Advanced Disease Management

* For metastatic or unresectable tumors, options include chemotherapy, targeted therapies, and palliative care to control symptoms.

## 7. Follow-up and Monitoring

* Regular monitoring of symptoms, serum VIP, electrolytes, and imaging to detect recurrence or progression.

## **TNM Staging Overview for VIPoma**

| **Stage** | **Description** |
| --- | --- |
| Stage I | Tumor confined to the pancreas, ≤2 cm in size (T1), no regional lymph node involvement (N0), no distant metastasis (M0). |
| Stage II | Tumor >2 cm or invading beyond pancreas but no nodal (N0) or distant metastasis (M0). |
| Stage III | Any tumor with regional lymph node metastasis (N1) or locally advanced tumor invading adjacent structures (T4), no distant metastasis (M0). |
| Stage IV | Presence of distant metastases (M1), commonly to the liver or other organs. |

## Grading

* VIPomas are graded based on differentiation and proliferation rate (Ki-67 index):
  + Grade 1: Well-differentiated, low proliferation, slow-growing
  + Grade 2: Intermediate grade
  + Grade 3: Poorly differentiated, high grade, fast-growing (rare in VIPomas)

**Genomic data on VIPoma**

* Gene location and function: The VIP gene is located on chromosome 6 and encodes the vasoactive intestinal peptide precursor. VIP acts via receptors on intestinal epithelial cells to increase cAMP, causing secretory diarrhea and other symptoms characteristic of VIPoma.
* Common genetic alterations in pancreatic NETs:
  + The most frequently mutated gene in PNETs is MEN1, involved in about 36–42% of cases overall. VIPomas, as functioning PNETs, show fewer MEN1 mutations (~9%) compared to non-functioning PNETs but still can be associated with MEN1 syndrome.
  + Other recurrent mutations in PNETs include DAXX and ATRX, genes involved in chromatin remodeling and telomere maintenance, though specific data on VIPomas are sparse.
  + Sporadic VIPomas are mostly not linked to hereditary syndromes, but familial cases occur in the context of MEN1.
* Molecular pathways: VIPomas secrete not only VIP but may also produce other substances like prostaglandin E2, contributing to symptoms. The regulation of VIP gene expression involves post-transcriptional mechanisms, which may be important in tumor biology.
* Genomic profiling studies: Large-scale genomic analyses of pancreatic NETs have identified mutations in tumor suppressor genes (MEN1, DAXX, ATRX) and pathways regulating cell cycle, chromatin remodeling, and DNA repair. However, specific mutational profiles for VIPomas are less well characterized due to their rarity.
* MEN1 association: VIPomas can be part of MEN1 syndrome, caused by germline mutations in the MEN1 gene, which predisposes to multiple endocrine tumors including VIPomas

**Doctor-patient conversation about VIPoma**

Doctor: "Based on your symptoms and test results, we believe you have a VIPoma. This is a rare type of tumor in your pancreas that produces a hormone called vasoactive intestinal peptide, or VIP."

Patient: "What does that hormone do, and how is it causing my symptoms?"

Doctor: "VIP normally helps regulate intestinal function, but when produced in excess by this tumor, it causes very large amounts of watery diarrhea, leading to dehydration, low potassium levels, and acid-base imbalances. This explains your persistent diarrhea and weakness."

Patient: "Is this tumor dangerous?"

Doctor: "VIPomas are considered highly malignant, and often by the time of diagnosis, they have spread to nearby lymph nodes or the liver. However, if we catch it early and the tumor is localized, surgical removal can be very effective."

Patient: "What will the treatment involve?"

Doctor: "First, we need to stabilize you by correcting dehydration and electrolyte imbalances with intravenous fluids and potassium. Then, we use medications called somatostatin analogs, like octreotide, which help reduce the hormone secretion and control diarrhea."

Patient: "And surgery?"

Doctor: "Yes, once you are stable, surgery to remove the tumor is the best option if it’s localized. In cases where the tumor has spread, surgery might still help reduce symptoms, but additional treatments like targeted therapies or liver-directed treatments may be needed."

Patient: "What about after treatment?"

Doctor: "You’ll need regular follow-up with blood tests and imaging to monitor for any recurrence or progression. Managing symptoms and maintaining your quality of life is a key part of ongoing care."

Patient: "Are there risks or side effects I should know about?"

Doctor: "Like any surgery, there are risks such as infection or bleeding, but these are minimized with modern techniques. Somatostatin analogs can cause side effects like gastrointestinal discomfort, but they are generally well tolerated. We will support you throughout your treatment."

Patient: "Thank you, this helps me understand what’s happening and what to expect."

Doctor: "You’re welcome. We’ll work closely together to manage your condition and keep you as comfortable as possible. Please feel free to ask any questions anytime."

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## **Pancreatic Neuroendocrine Tumors**

Pancreatic neuroendocrine tumors (pancreatic NETs, also called islet cell tumors) are rare tumors that start in your pancreas’ endocrine cells. They’re a type of neuroendocrine tumor.

Your pancreas is a flat pear-shaped gland tucked beside your stomach and small intestine. Endocrine cells in your pancreas make hormones that manage digestion and blood sugar levels.

These tumors can be cancerous (malignant) or benign (noncancerous). Without treatment, malignant tumors may spread to other areas of your body.

#### **Types of pancreatic neuroendocrine tumors**

There are several types of pancreatic NETs, each with different characteristics:

* Insulinomas are the most common type of functioning pancreatic NET. About 10% of insulinomas are cancerous. Insulinomas release insulin, the hormone that keeps your blood sugar from getting too high.
* Gastrinomas affect cells that release gastrin, which triggers your stomach to produce gastric acid. About 60% of gastrinomas are cancerous.
* Glucagonomas are often cancerous. They affect the cells that release glucagon, the hormone that keeps your blood sugar from getting too low.
* VIPomas can be cancerous. “VIP” stands for “vasoactive intestinal peptide.” This hormone relaxes the muscles in your stomach and bowels and manages the balance of sugar, salt and water in your digestive tract.
* Somatostatinomas are slow-growing cancerous tumors that release somatostatin. This hormone manages several bodily functions.

## **Symptoms and Causes**

Pancreatic NET symptoms may cause several different symptoms. Common symptoms include:

* Severe acid reflux
* Diarrhea
* Fatigue
* Frequent urination, increased thirst and other symptoms of swings in blood sugar levels
* Indigestion
* Loss of appetite
* Nausea and vomiting
* Uncomfortable flushing of your face and neck, wheezing and other carcinoid syndrome symptoms
* Unexplained weight loss
* Big swings in blood sugar, up or down

### **Pancreatic neuroendocrine tumor causes**

Researchers don’t know the exact cause. Some pancreatic NETs happen alongside other conditions. For example, about 5% to 10% of people with insulinomas or glucagonomas also have multiple endocrine neoplasia type 1 (MEN1).

### **Complications**

The most significant complication is that cancerous pancreatic NETs can spread (metastasize) to your bones, liver or lungs.

## **Diagnosis and Tests**

A healthcare provider will do a physical examination. They’ll ask about your symptoms. They may ask when your symptoms started and if they’re getting worse. They’ll also ask if anyone in your biological family has certain inherited disorders that increase pancreatic NET risk.

They may do the following tests:

* Abdominal computed tomography (CT) scan
* Blood tests, including specific tests for hormone levels, which can mean tumors are releasing lots of hormones
* Endoscopic ultrasound (EUS)
* Endoscopic retrograde cholangiopancreatography (ERCP)
* Magnetic resonance imaging (MRI)
* Neuroendocrine positron emission tomography (PET) scan

Providers use these test results to see if a tumor is functioning or non-functioning. Functioning tumors release unusually large amounts of hormones. Non-functioning tumors don’t release hormones. Test results also help providers identify the type of pancreatic neuroendocrine tumor.

Your provider may refer you to an interventional radiologist for a needle biopsy. This is a procedure to get tissue samples for lab tests. A medical pathologist will examine the tissue for signs of cancer.

#### **Pancreatic neuroendocrine tumor stages and grades**

Healthcare providers use cancer staging systems to set cancerous tumor stages and grades. Cancer stages describe tumor size and if the tumor is spreading to nearby lymph nodes or more distant areas of your body.

Cancer grades describe how fast the cells are multiplying. They also describe the cells’ appearance. Cancer cells’ appearance changes as the disease gets more aggressive.

The stages of cancerous pancreatic neuroendocrine tumors are:

* Stage I. The tumor measures less than 2 centimeters (cm) (about 3/4-inch) across and hasn’t spread from your pancreas.
* Stage II. It measures more than 2 cm (3/4-inch) across and/or has spread into your duodenum (the first part of your small intestine) or your bile ducts.
* Stage III. The tumor has spread to nearby lymph nodes, nearby organs or large blood vessels.
* Stage IV. The tumor is in more distant organs and tissues like your liver or bones.

Pancreatic NET grades are:

* Well-differentiated grade 1. Cancer cells aren’t multiplying very fast, and the cells look more like normal cells than abnormal cells.
* Well-differentiated grade 2. The cells have characteristics that fall in between those of low- and high-grade tumors.
* Well-differentiated grade 3. The cells are multiplying more quickly, and cells look more abnormal.
* Poorly differentiated NET. The cells are multiplying very quickly, and they look very abnormal. This is the most aggressive grade. Healthcare providers may call this grade high-grade neuroendocrine carcinoma (NEC) or small cell cancer.

## **Management and Treatment**

Treatment depends on your situation. Treatment for early-stage pancreatic NET is a pancreatectomy to remove the tumor. This is a treatment for cancerous and noncancerous tumors. Specific surgeries vary depending on the tumor’s location in your pancreas.

For example, your surgeon may use terms like “head” and “tail” when they talk about a specific surgery. That’s because your pancreas is shaped like a fish, with a wide head, a medium-sized middle or body, and a narrow tail. Common pancreatectomies are:

* Whipple procedure. This is the most common surgical treatment for pancreatic neuroendocrine tumors. In this procedure, surgeons remove the head of your pancreas and several nearby organs.
* Central pancreatomy. In this procedure, surgeons remove the central body part of your pancreas, leaving the pancreas’ head and tail.
* Distal pancreatomy. In this surgery, they remove your pancreas’ tail. They may remove part of the pancreas body and some or all of your spleen. (Your spleen and pancreatic tail are closely connected.)

Surgery may not be an option if you have an advanced form of pancreatic NET. Your oncologist may recommend other treatments, including:

* Hormone therapy
* Peptide receptor radionuclide therapy (PRRT)
* Tyrosine kinase inhibitors
* Chemotherapy

Your oncologist may recommend specific treatments for liver cancer if a pancreatic NET has spread to your liver.

#### **Recovery time**

Your recovery time will depend on the type of surgery you have. For example, it may take several weeks for you to recover from a Whipple procedure. You’ll be in the hospital for five to seven days and be able to get back to daily activities after eight to 12 weeks.

### **When should I contact my surgeon?**

You should see your healthcare provider if you notice changes in your body, like your original symptoms worsening. These changes might be unrelated to your condition. The best way to be sure is to talk to your provider.

## **Outlook / Prognosis**

Cancer survival rates are estimates of the percentage of people who were alive five years after they received a diagnosis. American Cancer Society data shows the following five-year survival rates:

| **Tumor location** | **Survival rate** |
| --- | --- |
| Localized, meaning a tumor that’s only in your pancreas | 95% |
| Regional, meaning there’s cancer in nearby tissues | 72% |
| Distant, meaning cancer has spread to more distant areas of your body | 23% |

When you think about survival rates, it’s important to remember that the rates reflect the overall experience of people with pancreatic neuroendocrine tumors. Factors like the kind of tumor, tumor stage, your age and your overall health make a difference.

Talk to your surgeon and oncologist if you have questions about survival rate data. They know you and your situation and are your best resource for information about what you can expect.

### **What’s the life expectancy for someone with a pancreatic neuroendocrine tumor?**

That’s hard to say. In general, people who are diagnosed with earlier-stage pancreatic NET and receive treatment before it spreads may have nearly normal life expectancies, particularly if they’re alive more than five years after diagnosis. Just like survival rates, your healthcare team is your best resource for information about your life expectancy.

**Differential diagnoses include:**

## 1. Pancreatic Ductal Adenocarcinoma (PDAC)

* Features: Hypovascular, poorly defined mass, often causing pancreatic duct obstruction and upstream atrophy.
* Imaging: PDAC typically shows delayed enhancement, ductal dilatation, and desmoplastic stroma, unlike the hypervascular and well-circumscribed PNETs.
* MRI sign: The “duct-road sign” and tumor-to-duct ratio (TDR) help differentiate PNETs from PDACs; PNETs have a higher TDR and positive duct-road sign.

## 2. Acinar Cell Carcinoma

* Features: Occurs in adults, aggressive, high mitotic rate.
* Immunohistochemistry: Positive for trypsin, chymotrypsin, BCL10; may show focal synaptophysin positivity but negative for chromogranin A (which is usually positive in PNETs).

## 3. Solid Pseudopapillary Neoplasm (SPN)

* Features: Typically affects young women, shows cystic and solid components, degenerative pseudopapillae, and hyaline globules.
* Immunohistochemistry: Nuclear beta-catenin positivity, usually chromogranin negative, may have focal synaptophysin positivity.

## 4. Pancreatoblastoma

* Features: Rare, mostly in children, characterized by squamoid nests and mixed differentiation.

## 5. Paraganglioma

* Features: Very rare in the pancreas, shows Zellballen architecture, cytokeratin negative, S100 positive sustentacular cells.

## 6. Cystic Pancreatic Neoplasms

* Includes mucinous cystic neoplasms, serous cystadenomas, and intraductal papillary mucinous neoplasms (IPMN), which have cystic morphology distinct from typically solid PNETs.

## 7. Accessory Spleen (Splenule)

* Can mimic small PNETs on imaging but follows the enhancement pattern of the spleen.

**Epidemiology of Pancreatic Neuroendocrine Tumors (pNETs):**

* Incidence:  
  Pancreatic neuroendocrine tumors are rare, with an annual incidence that has increased over recent decades. Current estimates from large population-based studies show incidence rates rising from about 0.27 to 1.0 per 100,000 people (SEER data from 2000 to 2016). Other studies report similar trends, with incidence nearly quadrupling over the last two decades. This rise is partly due to improved imaging techniques and increased incidental detection during abdominal scans for unrelated reasons.
* Prevalence:  
  pNETs account for less than 2-3% of all pancreatic cancers. Most pancreatic tumors are ductal adenocarcinomas, making pNETs relatively uncommon.
* Demographics:  
  The average age at diagnosis is around 60 years, with incidence increasing with age. There is a slight male predominance reported in some studies.
* Functional vs Non-functional Tumors:  
  Approximately 90% of pNETs are non-functional, meaning they do not produce clinical hormone syndromes, while about 10% are functional tumors producing hormones like insulin, gastrin, or VIP.
* Stage at Diagnosis and Survival:  
  There has been a notable stage migration with more patients diagnosed at localized stages in recent years, likely due to earlier detection.
  + Median overall survival (OS) is approximately 68 months, with 5-year survival rates of 83% for localized, 67% for regional, and 28% for metastatic disease.
  + Survival has improved significantly over time, with median OS increasing from 46 months (2000-2008) to 85 months (2009-2016), reflecting advances in diagnosis and treatment.
* Geographical and Global Trends:  
  Similar increasing incidence trends have been observed in Europe and North America, attributed to better diagnostics and classification systems

## **Mutated Genes and Pathways**

* MEN1 (Multiple Endocrine Neoplasia type 1 gene):
  + Located on chromosome 11q13.
  + Most frequently mutated gene in sporadic pNETs, with somatic mutations reported in about 25-44% of cases.
  + MEN1 encodes menin, a tumor suppressor involved in chromatin remodeling and transcription regulation.
* DAXX and ATRX:
  + Mutations in these genes occur in approximately 20-40% of pNETs.
  + Both genes are involved in chromatin remodeling and telomere maintenance by depositing histone variant H3.3 at telomeric and pericentromeric regions.
  + Loss of DAXX/ATRX is associated with alternative lengthening of telomeres (ALT) and correlates with worse prognosis.
* mTOR pathway genes:
  + Mutations in genes such as *TSC2*, *PTEN*, and *PIK3CA* are found in about 15-20% of well-differentiated pNETs.
  + These mutations activate the mTOR signaling pathway, promoting tumor growth and survival.
* VHL (Von Hippel-Lindau gene):
  + Mutated in pNETs associated with VHL syndrome, an inherited disorder increasing risk of pancreatic NETs.
  + VHL mutations affect hypoxia-inducible factor (HIF) regulation.
* Other genetic alterations:
  + Rare mutations in DNA damage repair genes such as *MUTYH*, *CHEK2*, *BRCA2*, and chromatin remodeling gene *SETD2* have been reported.
  + Copy number variations including gains in chromosomes 11p, 10q, 6q, 3p, 1p, 1q, 17q, 7q, 20q, and losses in chromosomes 3, 6q, and 1 are linked to metastatic risk.

## Molecular Subtypes and Cell of Origin

* Studies show two molecular subgroups of pNETs based on *MEN1*, *ATRX*, and *DAXX* mutation status:
  + A-D-M mutant tumors (mutations in ATRX, DAXX, MEN1): Represent about 58% of pNETs and have gene expression profiles similar to pancreatic alpha cells, suggesting an alpha-cell origin.
  + A-D-M wild-type tumors: May have beta-cell signatures or other origins.

**doctor-patient conversation about pancreatic neuroendocrine tumors**

Doctor: "Your tests show that you have a pancreatic neuroendocrine tumor, or PNET. This is a rare type of tumor that arises from hormone-producing cells in the pancreas."

Patient: "What does that mean? Is it cancer?"

Doctor: "PNETs can be either benign or malignant, but they are generally less aggressive than the more common type of pancreatic cancer. Some PNETs produce hormones that cause specific symptoms, while others do not. Your tumor’s behavior and treatment depend on its type, size, and whether it has spread."

Patient: "What are the treatment options?"

Doctor: "Treatment varies depending on your tumor’s characteristics. Surgery is the main treatment if the tumor can be removed. For tumors that produce hormones, medications called somatostatin analogues can help control symptoms. Other options include chemotherapy, targeted therapies, and sometimes procedures to treat liver metastases if the tumor has spread."

Patient: "Are there side effects or risks with these treatments?"

Doctor: "Like any treatment, there can be side effects. Surgery carries risks like infection or bleeding, but it can be curative. Medications may cause gastrointestinal discomfort or other mild side effects. We will monitor you closely and manage any side effects promptly."

Patient: "What happens after treatment?"

Doctor: "You will need regular follow-up visits with blood tests and imaging to monitor for any recurrence or progression. Many patients live for years with good quality of life, especially when the tumor is detected early."

Patient: "Is there anything I can do to prepare or help myself?"

Doctor: "It’s important to maintain a healthy lifestyle and keep all your appointments. If your tumor produces hormones, managing symptoms with medication and nutrition is key. We also encourage you to ask questions and bring a family member or friend to appointments for support."

Patient: "Thank you. This helps me understand what’s going on."

Doctor: "You’re welcome. We’ll work together to provide the best care possible. Please don’t hesitate to reach out with any questions or concerns."

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### **Metastasis**

Metastasis is when cancer spreads beyond the place where it started to other areas of your body. Nearly all cancers have the potential to metastasize. But whether they do depends on several factors — like the type, size and location of the primary tumor (where the cancer originated).

Metastases can occur in three ways. Cancer cells can:

1. Grow directly into the tissue surrounding the primary tumor.
2. Travel through your bloodstream to distant locations like other organs or your bones.
3. Move through your lymphatic system to nearby or distant lymph nodes.

Other names for metastasis include:

* Metastatic cancer.
* Stage IV (4) cancer.
* Secondary cancer.
* Cancer with mets (or mets cancer).

#### **Which cancers metastasize?**

Nearly all cancers can metastasize (spread). Some of the most common types include metastatic:

* Breast cancer.
* Colorectal cancer.
* Esophageal cancer.
* Lung cancer.
* Ovarian cancer.
* Pancreatic cancer.
* Prostate cancer.
* Skin cancers.
* Stomach cancer.
* Uterine cancer.

#### **Where does cancer metastasize first?**

Where cancer spreads during metastasis depends on the location of the primary (original) tumor. Some of the most common sites of metastases are the:

* Adrenal glands.
* Bones.
* Brain.
* Liver.
* Lungs.
* Lymph nodes.
* Peritoneum.

## **Symptoms and Causes**

Metastasis doesn’t always cause symptoms. Cancer cells can grow and spread gradually over many months or years. In some instances, it’s possible to have Stage IV (4) cancer and not know it.

General symptoms of metastasis may include:

* Extreme fatigue.
* Night sweats.
* Unexplained weight loss.

Some signs of metastatic cancer depend on the location of the primary tumor and where the cancer cells spread. Depending on the type of metastasis you have, symptoms might include:

* Bloating, swollen belly, decreased appetite, getting full quickly or jaundice (common in liver metastases).
* Bone pain or fractures (common in bone metastases).
* Dizziness, headaches and seizures (common in brain metastases).
* Shortness of breath (common in lung metastases).

### **What causes metastasis?**

Metastasis happens when cancer cells break off from the original tumor and spread to other parts of your body. These cancer cells can travel through your bloodstream or lymph vessels.

Many factors can trigger metastasis, like:

* A weakened immune system.
* Hypoxia (a lack of oxygen in your tissues).
* Lactic acidosis (a buildup of lactic acid in your blood).
* Autophagy (a type of cell death).

## **Diagnosis and Tests**

Some people already have metastatic cancer at the time of their diagnosis. In these cases, a healthcare provider usually detects metastases during initial testing.

Other people develop metastases after completing treatment for non-metastatic cancer. During routine follow-ups, a healthcare provider checks for signs of recurrence (cancer that comes back after treatment).

Your healthcare provider may use one or more of the following to diagnose metastatic cancer:

* Biopsy.
* Blood tests.
* Bone scans.
* CT (computed tomography) scans.
* MRI (magnetic resonance imaging) scans.
* PET (positron emission tomography) scans.
* Tumor marker-based tests.
* Ultrasound.
* X-rays.

## **Management and Treatment**

Healthcare providers can treat metastasis based on where the cancer started. For example, if a person has breast cancer and the cancer spreads to their liver, their provider will still treat it the same way as breast cancer. This is because the cancer cells haven’t changed — they’re just living in a new place.

Metastatic cancer treatments may include:

* Chemotherapy.
* Hormone therapy.
* Immunotherapy.
* Radiation therapy.
* Targeted therapy.

Some metastases may require local targeted therapy to manage symptoms. For instance, if you have breast cancer that spreads to the bone and causes pain or fractures, your provider can treat and ease those symptoms with surgery or radiation to the bone.

## **Outlook / Prognosis**

Your healthcare provider will work closely with you during cancer treatment and beyond. You’ll likely have many medical visits and will need to make important decisions regarding your overall health. Be sure to lean on friends, family and your healthcare team for support.

#### **Metastatic cancer life expectancy**

In most cases, metastatic cancer isn’t curable. But treatment can slow tumor growth and ease many of your symptoms. It’s possible to live for several years with some types of cancer, even after metastasis. Some metastases are potentially curable, including melanoma and colon cancer.

#### **Metastatic cancer survival rates**

The five-year survival rate depends on the type of metastases you have. For example, the five-year survival rate for metastatic lung cancer is 9%. This means that 9% of people diagnosed with metastatic lung cancer are still alive five years later. Meanwhile, the five-year survival rate of metastatic breast cancer is 30% for women and 19% for men.

It’s important to understand that survival rates are only estimates. They can’t tell you how you’ll respond to treatment or how long you’ll live. Ask your healthcare provider about survival rates for your specific condition.

## **Prevention**

You can’t always prevent cancer from spreading. But when providers can detect cancer earlier, a combination of surgery and adjuvant therapy might lower your risk for developing metastasis. Common adjuvant therapies include chemotherapy, targeted therapy and immunotherapy.

Experts continue to research ways to slow, stop or prevent the spread of cancer cells. But sometimes, metastasis happens, despite doing all the right things. According to research, there aren’t any diets that make people more prone to cancer or prevent metastasis from happening.

If you have metastatic cancer, it’s important to know that it’s not your fault and that you haven’t done anything wrong.

## **Living With**

A metastatic cancer diagnosis comes with many challenges. These challenges vary from person to person, but you might:

* Feel sad, angry or hopeless.
* Worry that treatment won’t work and that your cancer will get worse quickly.
* Get tired of going to so many appointments and making so many important decisions.
* Need help with daily routines.
* Feel frustrated about the cost of your treatment.

Talking with a counselor or social worker can help you cope with these complicated emotions. Managing stress is also an important aspect of self-care. Try practicing meditation or mindfulness, or find other ways to reduce stress and anxiety.

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

You should call your healthcare provider any time you develop new symptoms. Your cancer care team can adjust your treatment to meet your specific needs.

### **What questions should I ask my healthcare provider?**

Learning about your condition can empower you to make informed decisions. Here are some questions you may want to ask your healthcare provider:

## **Are there things I can do to improve my outlook?**

While metastatic cancer is often not curable, treatments can slow tumor growth, relieve symptoms, and improve quality of life, sometimes allowing people to live for several years. Staying as healthy as possible by eating well, staying active as tolerated, managing symptoms, and following your treatment plan can help improve your outlook. Early detection and treatment of complications are also important.

## **What are my treatment options?**

Treatment depends on the type of primary cancer, where it has spread, and your overall health. Common options include:

* Surgery (sometimes to remove tumors causing symptoms)
* Chemotherapy
* Radiation therapy
* Targeted therapies and immunotherapy (newer options that attack cancer cells more precisely)
* Hormonal therapies (for hormone-sensitive cancers)
* Palliative care to manage symptoms and side effects alongside other treatments.

Your doctor will tailor treatment to your specific situation, and if one treatment stops working, others may be available.

## **Are there clinical trial options I can explore?**

Yes. Many patients with metastatic cancer can participate in clinical trials testing new drugs or treatment combinations. Molecular testing of your tumor may identify specific mutations that qualify you for targeted therapies or trials. Ask your healthcare team about clinical trials available locally or at specialized centers.

## **Will palliative care continue even if I stop cancer treatments?**

Absolutely. Palliative care focuses on symptom relief, comfort, and quality of life and can be provided alongside active treatment or after stopping cancer-directed therapies. It supports physical, emotional, and spiritual needs throughout your illness.

## How often will I need to schedule follow-up appointments?

Follow-up schedules vary but typically involve regular visits every few weeks to months during active treatment to monitor response, side effects, and overall health. After treatment, follow-ups may be less frequent but continue lifelong to detect any progression or new symptoms.

## Do I need to consider hospice care?

Hospice care is a type of palliative care for people nearing the end of life, focusing on comfort and support rather than curative treatment. It is appropriate when cancer is no longer responding to treatment or when you choose to stop active therapy. Discuss with your healthcare team when and if hospice might be right for you.

## Should I choose a person to make medical decisions for me when I’m unable to make them for myself?

Yes, it’s important to designate a healthcare proxy or medical power of attorney—someone you trust to make decisions on your behalf if you become unable. This helps ensure your wishes are respected.

## What legal documents should I have in place?

Key documents include:

* Advance directive or living will (outlines your treatment preferences)
* Durable power of attorney for healthcare (appoints a decision-maker)
* Do Not Resuscitate (DNR) order, if desired  
  Your healthcare team or social worker can help you with these documents.

**Epidemiology of Metastatic Cancer:**

* Incidence and Prevalence:  
  Metastatic cancer refers to cancer that has spread from its original site to distant organs. It represents a significant portion of cancer burden worldwide. For example, in the United States:
  + The incidence of metastatic female breast cancer increased from 5.8 per 100,000 in 2001 to 7.9 per 100,000 in 2021.
  + In 2015, the overall incidence of metastatic cancers was about 53 per 100,000 individuals.
  + It is estimated that over 600,000 individuals were living with metastatic breast, prostate, lung, colorectal, bladder cancer, or metastatic melanoma in 2018 in the US.
  + The prevalence of metastatic cancers in the US is projected to rise to nearly 700,000 cases by 2025.
* Common Primary Cancers Leading to Metastasis:  
  The most frequent cancers that metastasize include:
  + Lung and bronchus cancer
  + Female breast cancer
  + Colorectal cancer
  + Prostate cancer
  + Melanoma
  + Bladder cancer
* Geographic and Socioeconomic Variation:
  + The prevalence of metastatic cancer at diagnosis varies globally, with higher rates reported in low- and middle-income countries (LMICs), sometimes exceeding 15-20% of cancer cases presenting with distant metastases at diagnosis.
  + In high-income countries like the US and many European nations, the prevalence of metastatic disease at diagnosis is generally lower, around 5-10% depending on cancer type.
* Mortality:
  + Metastatic cancer accounts for a large proportion of cancer-related deaths. For example, among metastatic cancer patients in the US, about 81% died during follow-up, mostly due to their metastatic disease.
  + Lung, colorectal, pancreatic, ovarian, and breast cancers are the leading causes of death among metastatic cancer patients.
* Trends:
  + The incidence and prevalence of metastatic cancers have generally increased over recent decades due to aging populations, improved detection, and better survival with some cancers.
  + Despite the increasing burden, 1- and 5-year survival rates have improved for many metastatic cancers except a few like bladder cancer

**Doctor-patient conversation about metastatic cancer**

Doctor:  
“Thank you for coming in today. I want to talk with you about your test results. The cancer has spread to other parts of your body — this is called metastatic cancer. I know this is difficult news, but I want to explain what this means and what we can do moving forward.”

Patient:  
“This sounds serious. What does it mean for me? What are my treatment options?”

Doctor:  
“Metastatic cancer means that the cancer cells have traveled from the original site to other organs. While this often means the cancer can’t be cured, there are many treatments available that can help control the disease, relieve symptoms, and improve your quality of life. These include surgery, chemotherapy, radiation, targeted therapies, and immunotherapy. We will tailor the treatment plan to your specific situation.”

Patient:  
“Will the treatment make me feel worse? What are the side effects?”

Doctor:  
“Every treatment has potential side effects, and we will discuss these carefully with you. Our goal is to balance controlling the cancer with maintaining your quality of life. We will monitor you closely and manage any side effects to keep you as comfortable as possible.”

Patient:  
“Is there anything I can do to improve my outlook?”

Doctor:  
“Staying as healthy as possible by eating well, staying active as you can, and managing symptoms helps. Also, following your treatment plan and attending all appointments is important. We will provide supportive care to help with pain, nausea, or other symptoms.”

Patient:  
“Are there clinical trials I could join?”

Doctor:  
“Yes, clinical trials can offer access to new treatments. We can review trials that might be suitable for you based on your cancer type and health. Participating in a trial is always your choice.”

Patient:  
“If I decide to stop treatment, will I still get care?”

Doctor:  
“Absolutely. Palliative care focuses on comfort and symptom relief and can continue alongside treatment or if you choose to stop cancer-directed therapies. Our team will support you and your family throughout.”

Patient:  
“How often will I need to come for appointments?”

Doctor:  
“That depends on the treatment plan, but usually appointments are scheduled every few weeks to monitor your response and adjust treatment as needed. We’ll make sure you know what to expect.”

Patient:  
“When should I think about hospice care?”

Doctor:  
“Hospice care is for when cancer is no longer responding to treatment, and the focus shifts entirely to comfort and quality of life. We will discuss this option with you when the time is right, based on your preferences and health status.”

Patient:  
“Should I choose someone to make medical decisions if I can’t?”

Doctor:  
“Yes, it’s very helpful to designate a trusted person as your healthcare proxy or medical power of attorney. This person can make decisions for you if you’re unable. We can help you with the paperwork.”

Patient:  
“What legal documents should I have?”

Doctor:  
“An advance directive or living will, durable power of attorney for healthcare, and if you wish, a Do Not Resuscitate (DNR) order. Our social worker or patient navigator can assist you with these.”

Patient:  
“Are there resources to help me cope with all this?”

Doctor:  
“Definitely. We can connect you with support groups, counseling services, educational materials, and patient navigators who can help you and your family through this journey.”

Patient:  
“Thank you for explaining everything clearly. It helps to know what to expect.”

Doctor:  
“You’re welcome. We’re here to support you every step of the way. Please feel free to ask questions anytime.”

REFERENCES

<https://www.cancer.ie/cancer-information-and-support/cancer-types/metastatic-cancer/metastatic-cancer-treatment>

[What Is Metastasis? (Stage IV, Metastatic or Secondary Cancer)](https://my.clevelandclinic.org/health/diseases/22213-metastasis-metastatic-cancer#overview)

<https://www.cdc.gov/united-states-cancer-statistics/publications/metastatic-breast-cancer.html>

### **Langerhans cell histiocytosis**

Langerhans cell histiocytosis (LCH) is a rare disorder that primarily affects babies and children. The disorder occurs when immune system cells called Langerhans cells build up in your child’s body. Langerhans cells are a type of white blood cell that helps your child’s immune system fight infection.

Your child has Langerhans cells throughout their body, especially in their skin, lungs, lymph nodes, bone marrow, spleen and liver. When there’s a buildup of these cells, it can damage your child’s tissues and cause lesions to form in one or more places in their body.

The outlook (prognosis) of Langerhans cell histiocytosis is wide-ranging, but in general, is good. For many children with LCH, the disease goes away with appropriate treatment. In fact, it may go away on its own, especially if it only occurs in your child’s skin. But when LCH affects your child’s bone marrow, spleen or liver, the disease may require intensive therapy.

#### **Is Langerhans cell histiocytosis cancer?**

Many researchers consider Langerhans cell histiocytosis a type of neoplasm. But some have begun to consider it an inflammatory disease. Healthcare providers who treat cancer and blood disorders (oncologists) also treat Langerhans cell histiocytosis. Sometimes, oncologists use cancer therapies like chemotherapy to treat the condition.

Most cases of LCH affect newborns and children between the ages of 1 and 15 years old. Langerhans cell histiocytosis in adults is rare, but it can occur.

Langerhans cell histiocytosis occurs in 1 to 2 out of every 1 million newborns every year. It affects about 5 out of every 1 million children ages 15 and younger each year.

## **Symptoms and Causes**

Langerhans cell histiocytosis varies greatly from person to person. It may involve only one part of your child’s body or many different sites. So, Langerhans cell histiocytosis symptoms will vary depending on which part of your child’s body is affected.

#### **Bones**

In about 80% of children with LCH, one or more lesions develop in their bones. This can cause swelling or a lump over a bone like your child’s skull, eye socket, ear bone, jaw bone, arms, legs, spine, hips or ribs. The swelling may or may not be painful. Additional symptoms affecting bones may include:

* Headaches.
* Neck pain or back pain.
* Fractures.
* Difficulty walking.
* Limping.

#### **Skin**

Langerhans cell histiocytosis skin symptoms typically include a rash. In infants, it may be a scalp rash that looks like cradle cap. In children and adults, a flaky rash may look like dandruff. Rashes may appear on other parts of your child’s body and be tender, painful or itching. Your child may have oozing blisters. Other areas of their body that may be affected include:

* Groin.
* Arms.
* Armpits.
* Abdomen.
* Back.
* Chest.

In addition, you may notice discoloration or hardening of your child’s nails or their nails may fall out.

#### **Mouth**

Symptoms of Langerhans cell histiocytosis that may affect your child’s mouth include:

* Loose teeth or teeth that fall out.
* Uneven teeth.
* Swollen gums.
* Sores on their lips, tongue, inside their cheeks or on the roof of their mouth.

#### **Liver or spleen**

Symptoms of LCH that may affect your child’s liver and/or spleen include:

* Swelling of their belly (abdomen) due to an enlarged liver and/or spleen.
* Yellowing of their skin and whites of their eyes (jaundice).
* Itchiness.
* Fatigue.
* Easy bruising and/or bleeding.

#### **Bone marrow**

Signs of LCH that may affect your child’s bone marrow include:

* Anemia, pale skin, fatigue and decreased appetite due to low red blood cells.
* Frequent infections and fevers due to low white blood cells.
* Easy bruising and/or bleeding due to low platelets (clotting cells).

#### **Endocrine system (hormones)**

Langerhans cell histiocytosis may affect your child’s endocrine system, including their pituitary gland and their thyroid gland. Symptoms that may affect these glands include:

* Pituitary gland: Excessive thirst (polydipsia) and frequent urination due to diabetes insipidus, slow growth, early or late puberty and weight gain.
* Thyroid gland: Swollen thyroid, signs of hypothyroidism and difficulty breathing.

#### **Ears**

Symptoms of LCH that may affect your child’s ears include:

* Chronic infections.
* Discharge from their ear canal.
* Redness.
* Itchy rash.
* Ear pain.
* Hearing loss.

#### **Eyes**

Signs of Langerhans cell histiocytosis that may affect your child’s eyes include:

* Bulging eyes.
* Swelling above their eyes.
* Vision problems.

#### **Lymph nodes**

Signs of LCH that may affect your child’s lymph nodes include:

* Swollen, tender lymph nodes in their neck, armpits and/or groin.

#### **Central nervous system**

Symptoms of LCH that may affect your child’s brain and/or spinal cord (central nervous system) include:

* Headaches.
* Dizziness.
* Vomiting.
* Excessive thirst.
* Frequent urination.
* Difficulty walking.
* Loss of balance.
* Uncoordinated body movements (ataxia).
* Difficulty speaking or seeing.
* Seizures.
* Changes in behavior and/or memory.

#### **Lungs**

Lung (pulmonary) Langerhans cell histiocytosis is more prevalent in adults. People who smoke are at a higher risk of developing pulmonary LCH. Signs of LCH in your lungs include:

* Chest pain.
* Dry cough.
* Difficulty breathing.
* Coughing up blood.
* Collapsed lung (pneumothorax).

#### **Gastrointestinal tract**

Symptoms of Langerhans cell histiocytosis that may affect your child’s stomach, intestines and/or colon may include:

* Abdominal pain.
* Vomiting.
* Diarrhea.
* Bloody poop (stools).
* Growth delay due to low nutrition.

Because the cause of these symptoms could be another condition not related to Langerhans cell histiocytosis, it’s important to seek proper medical attention to receive an accurate diagnosis.

### **What causes Langerhans cell histiocytosis?**

In about half of the people with LCH, a somatic mutation in the *BRAF* gene causes the condition. A somatic mutation is a change that occurs in certain cells after conception. (You don’t inherit these mutations — they happen randomly to a developing fetus.)

The *BRAF* gene is responsible for making a protein that controls cell growth and development. Normally, this protein can be switched on and off in response to chemical signals. A mutation in this gene causes the protein to be stuck in the “on” position, which causes too many LCH cells to grow and divide. This can cause tissue damage and the formation of tumors.

Scientists have discovered mutations in other genes that can lead to the disease as well. These include the *MAP2K1*, *RAS* and *ARAF* genes. Some researchers believe other factors, like environmental toxins and viral infections, may also lead to the development of the disorder.

#### **Risk factors for Langerhans cell histiocytosis**

Certain factors put your child at a higher risk of developing Langerhans cell histiocytosis. These include:

* Family history of LCH.
* Being Hispanic.
* Smoking.
* Exposure to certain chemicals during pregnancy.
* Exposure to metal, granite or wood dust in the workplace.
* Having infections as a newborn.
* Not receiving vaccinations as a child.

### **Complications of Langerhans cell histiocytosis**

Almost 50% of children with Langerhans cell histiocytosis will experience complications due to the condition, including:

* Scarring.
* Growth delay.
* Musculoskeletal disability.
* Diabetes insipidus.
* Hormonal imbalances.
* Hearing loss.
* Mental health conditions like depression and anxiety.
* Bone and lung issues.
* Liver cirrhosis.
* Secondary cancers, like leukemia, lymphoma and Ewing sarcoma.

## **Diagnosis and Tests**

Your child's healthcare provider will ask about your child’s medical history and perform a physical exam. They’ll request several tests, depending on where your child has symptoms. Based on their findings, your child’s provider may refer you to a pediatric hematologist/oncologist, who’ll coordinate the care and treatment of your child.

#### **What tests will be done to diagnose this condition?**

Langerhans cell histiocytosis can affect many different parts of your child’s body. Therefore, your child may need several tests to diagnose the condition.

#### **Blood tests**

* Complete blood count (CBC): A CBC is a blood test that checks your child’s levels of red blood cells, white blood cells and platelets.
* Blood chemistry tests: A blood chemistry study is a blood sample that looks at the amount of certain substances released into your child’s body by their organs and tissues.
* Liver function tests: A liver function test is a blood test that checks your child’s levels of substances released by their liver.

#### **Urine tests**

* Urinalysis: A urinalysis is a test that checks the amount of red blood cells, white blood cells, proteins and sugar in your child’s pee (urine).
* Water deprivation test: A water deprivation test checks how much urine your child makes and whether it becomes concentrated when water is withheld.

#### **Biopsies**

* Biopsy: During a biopsy, a healthcare provider will remove a sample of tissue. A pathologist will look at the sample under a microscope to check for LCH cells.
* Bone marrow aspiration and biopsy: A healthcare provider will insert a hollow needle into your child’s hipbone to remove a sample of bone marrow, blood and a small piece of bone. A pathologist will look at the sample under a microscope.

#### **Genetic testing**

* Genetic testing: Genetic testing uses a blood or tissue sample to look for changes in the *BRAF* gene.

#### **Imaging tests**

* X-rays: X-rays are images of the bones and organs inside your child’s body. A healthcare provider may sometimes take X-rays of all the bones in your child’s body (skeletal survey) to look for abnormalities.
* Bone scan: During a bone scan, a provider will inject a small amount of radioactive material into your child’s vein. This material collects in any abnormal parts of bone and shows up on the scanner. This imaging test is rare.
* Computed tomography (CT) scan: For this procedure, your child may swallow a dye or a provider may inject the dye into a vein. The scan takes detailed pictures of areas inside your child’s body at different angles.
* Positron emission tomography (PET) scan: A provider will inject a small amount of radioactive sugar (glucose) into your child’s vein. The scanner will rotate around your child’s body and take pictures of where glucose is being used. The glucose makes any diseased cells show up brighter on the scanner.
* Magnetic resonance imaging (MRI) scan: A healthcare provider will inject a substance called gadolinium into a vein, and diseased areas will show up brighter on the scan. An MRI uses magnets, radio waves and a computer to make a series of detailed pictures.
* Ultrasound: An ultrasound scan uses high-energy sound waves that bounce off your child’s organs and tissues and make echoes. This forms internal pictures of your child’s body.

## **Management and Treatment**

Treatment for Langerhans cell histiocytosis depends on where LCH cells are located in your child’s body and whether the condition is considered low-risk or high-risk.

Low-risk organs include:

* Skin.
* Bone.
* Lungs.
* Lymph nodes.
* Gastrointestinal tract.
* Pituitary gland.
* Thyroid gland.
* Thymus.

High-risk organs include:

* Liver.
* Spleen.
* Bone marrow.
* Central nervous system (CNS).

Healthcare providers classify LCH as single-system disease or multi-system disease. They classify the disease based on how many of your child’s body systems are affected:

* Single-system LCH: One part of an organ or body system contains LCH cells. The most common type of single-system LCH is bone LCH.
* Multi-system LCH: Two or more organs or body systems contain LCH cells or LCH cells are throughout your child’s body. Multi-system LCH is less common than single-system LCH.

In certain cases, LCH may improve on its own without treatment. This typically occurs in single-system LCH cases involving the skin or bone. In these cases, treatment involves observation to ensure the disease doesn’t return or spread.

#### **Langerhans cell histiocytosis treatment**

Treatment options for LCH may include:

* Steroid therapy: Your child’s healthcare provider may use a steroid like prednisone, particularly for skin LCH. Prednisone hinders the functioning of white blood cells, which could affect the LCH cells.
* Surgery: Your child’s provider may use surgery to remove LCH tumors and surrounding tissue. They use a procedure called curettage. Curettage is a type of surgery that uses a sharp, spoon-shaped tool called a curette to scrape LCH cells from bone.
* Chemotherapy: Chemotherapy uses drugs to stop the growth of neoplastic cells, either by killing them or by preventing them from dividing. Your child may take chemotherapy by mouth or a provider may inject it into a vein or muscle. You may apply a chemotherapy cream or lotion directly onto the skin as well.
* Radiation therapy: Radiation therapy uses high-energy X-rays and other types of radiation to kill cancer cells or prevent them from growing and dividing.
* Immunotherapy: Immunotherapy uses your child’s immune system to fight cancer. A provider will use substances made by your child’s body or made in a laboratory to boost, direct or restore their body’s natural defenses.
* Targeted therapy: Targeted therapy uses drugs or other substances to identify and attack specific cancer cells. Types of targeted therapy include BRAF inhibitors, which block proteins needed for cell growth and may kill cancer cells, and monoclonal antibodies, which are immune system proteins made in a laboratory to treat diseases such as cancer.
* Stem cell transplant: A stem cell transplant replaces your child’s blood-forming cells that are killed during chemotherapy treatment.

## **Outlook / Prognosis**

The prognosis for LCH depends on various factors, including:

* How many body systems or organs are affected.
* Which body systems or organs are affected?
* How well the disease responds to treatment.

Typically, providers consider children with single-system LCH and multi-system LCH that doesn’t involve the liver, spleen or bone marrow low risk. With treatment, the overall survival rate for children in this category is 100%. However, disease recurrence and/or other long-term complications are common.

Providers consider children with multi-system LCH that involve the liver, spleen or bone marrow high risk.

## **Prevention**

You can’t prevent Langerhans cell histiocytosis because a genetic mutation causes it. Some risk factors for LCH are things you can’t control like your biological family history and ethnicity. But there are some factors you can manage, like:

* Not smoking.
* Avoiding certain chemicals while pregnant.
* Getting all of your recommended vaccinations.

### **When should my child see their healthcare provider?**

Even after your child completes treatment, their healthcare provider will want to see them regularly. They’ll want to monitor your child for many years because the disease has a high risk of coming back (recurring). At their follow-up appointments, your child will repeat many of the same tests they had when they received their diagnosis. These may include ultrasounds, MRIs, CT scans and PET scans. Your child’s provider will let you know how often you need to come back for follow-up.

### **What questions should I ask my child’s provider?**

You may have many questions about your child’s diagnosis. It may help to write them down to take with you to your child’s next appointment. A few questions you may want to ask include:

## How Does Langerhans Cell Histiocytosis Affect My Child?

LCH can affect various parts of the body, including the skin, bones, liver, lungs, brain, spleen, lymph nodes, teeth and gums, eyes, central nervous system, ears, and pituitary gland . Symptoms can range from mild to severe. Common signs include:

* Skin: Red, scaly scalps (sometimes confused with cradle cap) and red, scaly bumps in skin folds .
* Bone: Bone lesions, pain, and a limp .
* Liver: In severe cases, jaundice and slower blood clotting .
* Lymph nodes: Inflammation behind the ears or in the neck, sometimes leading to breathing issues and cough .
* Lungs: Non-productive cough and shortness of breath, and less frequently, chest pain, general malaise, and fatigue .
* Teeth and Gums: Gum swelling and potential tooth loss .
* Eyes: Vision issues or bulging eyes .
* Central Nervous System (CNS): Chronic headaches, dizziness, vomiting, excessive thirst, and frequent urination .
* Ear: Frequent infections and discharge .
* Pituitary Gland: Affects hormone production, potentially causing delayed puberty, infertility, excessive urination, and thyroid problems .

## Does My Child Need Treatment?

Treatment for LCH varies widely, and in some cases, no treatment is necessary as the disease may resolve on its own, particularly in single-system LCH involving only the skin or bone . In these instances, watchful waiting and observation are often employed to ensure the disease does not return or spread .

## What Are My Child’s Treatment Options?

If treatment is needed, it will be determined by factors such as your child's age, overall health, the extent of the disease, and tolerance for therapies . Treatment options include:

* Surgery: Initially used for biopsy, and sometimes to remove all LCH cells. Further surgery may be needed to remove remaining cells .
* Medication:
  + Steroids (e.g., prednisone): Can lessen bone pain and may be used to suppress the immune system, especially for skin LCH .
  + Nonsteroidal Anti-inflammatories (NSAIDs): Such as indomethacin, for bone pain .
* Chemotherapy: Works by interfering with the growth and reproduction of abnormal cells. It can be given orally, subcutaneously, or intravenously . Chemotherapy for LCH is usually mild, with children rarely becoming very sick .
* Radiation Therapy: Rarely used, but small doses may be employed to stop Langerhans cell growth in specific areas .
* Photodynamic therapy: Another treatment option .
* Organ and Tissue Transplants: In severe cases, particularly involving the lungs, liver, or bone marrow .
* Ultraviolet Light Therapy: To treat skin conditions associated with LCH .

A multidisciplinary team, including hematologist/oncologists, dermatologists, pulmonologists, endocrinologists, and others, often works together to determine the best approach .

## What Are the Side Effects of Treatment?

The provided search results do not detail the specific side effects for each treatment option. However, chemotherapy for LCH is generally described as mild, with children rarely experiencing severe sickness or needing intensive treatment .

## Will These Treatments Cure My Child?

Most children with LCH make a full recovery after treatment . However, disease recurrence and/or other long-term complications are common . Regular follow-up appointments are necessary for many years due to the high risk of recurrence .

## What Is My Child’s Prognosis?

The prognosis for LCH depends on various factors, including the stage of the disorder, the treatment provided, your child’s general health, and age .

* Low-risk LCH: This category includes single-system LCH and multi-system LCH that does not involve the liver, spleen, or bone marrow. With treatment, the overall survival rate for children in this category is 100% .
* High-risk LCH: This involves multi-system LCH affecting the liver, spleen, or bone marrow. For children in this category, there is an 80% survival rate .

## Can You Recommend Any Support Groups?

The provided search results do not specifically recommend support groups. However, you can inquire with your child's healthcare team at Dana-Farber/Boston Children's Histiocytosis Program or Stanford Children's Health , as they are likely to have resources or connections to relevant support organizations.

## **Diagnostic Considerations**

Consider the following in the differential diagnosis of Langerhans cell histiocytosis:

* Rosai-Dorfman disease
* Xanthoma disseminatum
* Neonatal pustular melanosis
* Congenital candidiasis
* Perinatal listeriosis
* Perinatal herpes simplex
* Neonatal varicella
* Leukemia
* Lymphoma
* Myeloma
* Malignant melanoma

**DIFFERENTIAL DIAGNOSIS**

The differential diagnoses of LCH include the following:

* Acrodermatitis enteriropathica
* Acropustulosis of infants
* Congenital candidiasis
* Eosinophilic pustular folliculitis
* Incontinentia pigmenti
* Leukaemia
* Lymphoma
* Mastocytosis
* Myeloma
* Neonatal pustular melanosis

## **Epidemiology**

### Frequency

Langerhans cell histiocytosis (LCH) is a rare disease. The estimated annual incidence ranges from 0.5-5.4 cases per million persons per year. Approximately 1200 new cases per year are reported in the United States.

### Race-, sex-, and age-related demographics

The prevalence of LCH seems to be higher among whites than in persons of other races.

The frequency of LCH is greater in males than in females, with a male-to-female ratio of ~ 2:1.

LCH affects patients from the neonatal period to adulthood, although it appears to be more common in children aged 0-15 years (reportedly approximately 4 cases per million population).The age at onset varies according to the variant of LCH, as follows [4] :

* Letterer-Siwe disease occurs predominantly in children younger than 2 years.
* The chronic multifocal form, including Hand-Schüller-Christian syndrome, has a peak of onset in children aged 2-10 years.
* Localized eosinophilic granuloma occurs mostly frequently in children aged 5-15 years.
* Pulmonary LCH is more common during the third and fourth decades of life

## **Staging**

The Histiocyte Society stratifies patients with Langerhans cell histiocytosis (LCH) into single-system LCH (SS-LCH) or multisystem LCH (MS-LCH).

SS-LCH includes involvement of one of the following systems (either unifocal or multifocal involvement):

* Bone
* Skin
* Lymph Node
* Lungs
* Central nervous system
* Other (eg, thyroid, thymus)

MS-LCH is defined as involvement of 2 or more organs or organ systems, irrespective of involvement of "risk organs." The following organ systems are classified as risk organs, and their involvement indicates a worse prognosis:

* Spleen
* Liver
* Hematopoietic system
* Lung

## **Medication**

The goals of pharmacotherapy for Langerhans cell histiocytosis (LCH) are to reduce morbidity and to prevent complications.

## Corticosteroids

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These agents have anti-inflammatory properties and cause profound and varied metabolic effects. Corticosteroids modify the body's immune response to diverse stimuli.

## Prednisone (Deltasone, Prednisone Intensol, Rayos)

Prednisone may decrease inflammation by reversing increased capillary permeability and suppressing PMN activity.

Use the lowest effective dose in elderly patients. Pediatric dosing depends on the condition being treated and the response of the patient; the dose for infants and children should be based on severity and the response of the patient rather than on strict adherence to the dose indicated by age, weight, or body surface area.

## Prednisolone (FloPred, Millipred, Millipred DP)

Prednisolone is also known as delta hydrocortisone, metacortandralone, prednisolone acetate, and prednisolone sodium phosphate. It decreases inflammation by suppressing the migration of polymorphonuclear leukocytes and reducing capillary permeability.

## Methylprednisolone (A-Methapred, DepoMedrol, Medrol)

Methylprednisolone is also known as 6-alpha-methylprednisolone, methylprednisolone acetate, and methylprednisolone sodium succinate. By reversing increased capillary permeability and suppressing PMN activity, it may decrease inflammation.

## **Nonsteroidal anti-inflammatory drugs**

These agents are the most commonly used medications to control mild to moderate pain and to decrease inflammation.

## Indomethacin (Indocin, Indocin SR (DSC), Tivorbex (DSC))

Indomethacin is rapidly absorbed; metabolism occurs in the liver by demethylation, deacetylation, and glucuronide conjugation; it inhibits prostaglandin synthesis.

## **Antineoplastic agents**

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These agents inhibit cell growth and proliferation.

## Mechlorethamine (Mechlorethamine hcl, Mustargen, Nitrogen Mustard)

Mechlorethamine forms interstrand and intrastrand cross-links in DNA, which, in turn, results in miscoding, breakage, and failure of replication, inhibiting cell growth. It is dispensed as either an aqueous solution or an ointment. The contents of a 10-mg vial are rehydrated with 50 mL of tap water. The patient should wear protective plastic gloves while applying the solution. Unused preparation may be stored in the refrigerator.

## Vinblastine (Velban)

Vinblastine inhibits microtubule formation, which, in turn, disrupts the formation of a mitotic spindle, causing cell proliferation to arrest at metaphase.

## 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 the cell cycle.

## Mercaptopurine (6Mercaptopurine, 6MP, Purinethol)

Mercaptopurine is a purine analog that inhibits DNA and RNA synthesis, causing cell proliferation to arrest.

## Methotrexate (Jylamvo, Otrexup, Rasuvo)

Methotrexate is an antimetabolite that inhibits DNA synthesis and cell reproduction in malignant cells. Adjust the dose gradually to attain a satisfactory response. Refer to individual protocols; it may be administered through various routes.

## Cladribine (Leustatin DSC, Mavenclad)

Cladribine (2-chlorodeoxyadenosine [2-CdA]) is a synthetic antineoplastic agent for continuous intravenous infusion. The enzyme deoxycytidine kinase phosphorylates this compound into active 5+-triphosphate derivative, which, in turn, breaks DNA strands and inhibits DNA synthesis. It disrupts cell metabolism, causing death to resting and dividing cells.

## Cytarabine (Cytosar U, DepoCyt)

Cytarabine is converted intracellularly to the active compound cytarabine-5'-triphosphate, which inhibits DNA polymerase. It is cell-cycle S-phase specific. Cytarabine blocks the progression from G1 to the S phase and, in turn, kills cells that undergo DNA synthesis in the S phase of the cell proliferation cycle.

## Vemurafenib (Zelboraf)

Vemurafenib is an inhibitor of some mutated forms of *BRAF* serine-threonine kinase, including *BRAF*-V600. It is indicated for Erdheim-Chester disease (ECD) with *BRAF* V600 mutation. This is the first FDA-approved treatment for ECD.

## Cobimetinib (Cotellic)

Indicated for adults with histiocytic neoplasms eg, (Langerhans cell histiocytosis, Roasi-Dorfman, Erdheim-Chester disease). It is a reversible inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase 1 (MEK1) and MEK2. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation.

## **Phototherapy agents**

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PUVA has been a successful therapy for some patients. The goal of treatment is to induce remission of skin diseases by repeated and controlled phototoxic reaction. Photoconjugation of psoralens with DNA produces an antiproliferative reaction in the skin, generates programmed cell death (apoptosis), and induces down-regulation of the cutaneous immune system.

## Methoxsalen (8MOP, Oxsoralen, Oxsoralen Ultra)

Methoxsalen inhibits mitosis by binding covalently to pyrimidine bases in DNA when photoactivated by ultraviolet-A (UV-A) light. Doses are based on lean body weight.

## **Bisphosphonate derivatives**

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These agents inhibit bone resorption by osteoclasts and in turn mitigate associated bone pain.

## Zoledronic acid (Reclast, Zometa)

Zoledronic acid is used to treat multiple myeloma and solid tumor bone metastases. It is also used for hypercalcemia of malignancy. It inhibits bone resorption, possibly by acting on osteoclasts or osteoclast precursors. The median duration of complete response (maintaining normalized calcium levels) and time to relapse is reported as 32 and 30 days, respectively. Administer daily calcium and vitamin D when used for multiple myeloma or metastatic bone disease.

**Doctor-patient conversation about Langerhans Cell Histiocytosis (LCH)**

Doctor: "I want to talk with you about your child's diagnosis of Langerhans Cell Histiocytosis, or LCH. It’s a rare disorder where certain immune cells called Langerhans cells grow abnormally and can affect different parts of the body."

Parent: "Is it cancer? How serious is it?"

Doctor: "LCH is sometimes described as a cancer-like condition because it involves abnormal cell growth, but it behaves differently from typical cancers. The seriousness depends on how many organs are involved and which ones. Some children have only one area affected, like a single bone lesion or skin rash, and others may have multiple organs involved."

Parent: "What kind of treatment will my child need?"

Doctor: "Treatment depends on the extent of the disease. For limited skin or bone involvement, sometimes no treatment is needed, or we may use topical therapies or surgery to remove lesions. If multiple organs are involved, systemic treatments like chemotherapy or steroids may be necessary. We tailor treatment to your child’s specific situation."

Parent: "Are there side effects from the treatment?"

Doctor: "Most children tolerate treatment well. Chemotherapy used for LCH tends to be milder than for other cancers, but side effects can include fatigue, nausea, or increased risk of infection. We will monitor your child closely and manage any side effects promptly."

Parent: "Will my child be cured?"

Doctor: "Many children with LCH do very well and can be cured, especially those with single-system disease. However, some cases can recur or cause long-term effects, so regular follow-up is important to monitor and manage any issues early."

Parent: "What is the outlook for my child?"

Doctor: "The prognosis varies. Children with disease limited to one system generally have excellent outcomes. Those with multisystem involvement, especially affecting organs like the liver or bone marrow, require more intensive treatment but still have a good chance of survival with modern therapies."

Parent: "Are there support groups or resources for families like ours?"

Doctor: "Absolutely. There are organizations such as the Histiocytosis Association that offer education, support groups, and connections with other families. They also provide access to specialists and clinical trials. I can give you their contact information and help you get connected."

Parent: "What can I do to help my child through this?"

Doctor: "Being part of the care team is very important. Keep track of symptoms, attend all appointments, and communicate openly with us. Emotional support for your child and family is also vital, and we can connect you with counseling or child life specialists."

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**CARCINOID TUMOR**

**DEFINITION AND DESCRIPTION**

Carcinoid tumors are a type of slow-growing cancer that can arise in several places throughout your body. Carcinoid tumors, which are one subset of tumors called neuroendocrine tumors, usually begin in the digestive tract (stomach, appendix, small intestine, colon, rectum) or in the lungs.

Carcinoid tumors often don't cause signs and symptoms until late in the disease. Carcinoid tumors can produce and release hormones into your body that cause signs and symptoms such as diarrhea or skin flushing.

Treatment for carcinoid tumors usually includes surgery and may include medications.

**Symptoms**

Some carcinoid tumors don't cause any signs or symptoms. When they do occur, signs and symptoms are usually vague and depend on the location of the tumor.

### **Carcinoid tumors in the lungs**

Signs and symptoms of carcinoid lung tumors include:

* Chest pain
* Wheezing
* Shortness of breath
* Diarrhea
* Redness or a feeling of warmth in your face and neck (skin flushing)
* Weight gain, particularly around the midsection and upper back
* Pink or purple marks on the skin that look like stretch marks

### **Carcinoid tumors in the digestive tract**

Signs and symptoms of carcinoid tumors in the digestive tract include:

* Abdominal pain
* Diarrhea
* Nausea, vomiting and inability to pass stool due to intestinal blockage (bowel obstruction)
* Rectal bleeding
* Rectal pain
* Redness or a feeling of warmth in your face and neck (skin flushing)

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

If you experience any signs and symptoms that bother you and are persistent, make an appointment with your doctor.

**Causes**

It's not clear what causes carcinoid tumors. In general, cancer occurs when a cell develops mutations in its DNA. The mutations allow the cell to continue growing and dividing when healthy cells would normally die.

The accumulating cells form a tumor. Cancer cells can invade nearby healthy tissue and spread to other parts of the body.

Doctors don't know what causes the mutations that can lead to carcinoid tumors. But they know that carcinoid tumors develop in neuroendocrine cells.

Neuroendocrine cells are found in various organs throughout the body. They perform some nerve cell functions and some hormone-producing endocrine cell functions. Some hormones that are produced by neuroendocrine cells are histamine, insulin and serotonin.

**Risk factors**

Factors that increase the risk of carcinoid tumors include:

* **Older age.** Older adults are more likely to be diagnosed with a carcinoid tumor than are younger people or children.
* **Sex.** Women are more likely than men to develop carcinoid tumors.
* **Family history.** A family history of multiple endocrine neoplasia, type 1 (MEN 1), increases the risk of carcinoid tumors. In people with MEN 1 multiple tumors occur in glands of the endocrine system.

**Complications**

The cells of carcinoid tumors can secrete hormones and other chemicals, causing a range of complications including:

* **Carcinoid syndrome.** Carcinoid syndrome causes redness or a feeling of warmth in your face and neck (skin flushing), chronic diarrhea, and difficulty breathing, among other signs and symptoms.
* **Carcinoid heart disease.** Carcinoid tumors may secrete hormones that can cause thickening of the lining of heart chambers, valves and blood vessels. This can lead to leaky heart valves and heart failure that may require valve-replacement surgery. Carcinoid heart disease can usually be controlled with medications.
* **Cushing syndrome.** A lung carcinoid tumor can produce an excess of a hormone that can cause your body to produce too much of the hormone cortisol.

## **Diagnosis**

Tests and procedures used to diagnose carcinoid tumors include:

* **Blood tests.** If you have a carcinoid tumor, your blood may contain high levels of hormones secreted by a carcinoid tumor or byproducts created when those hormones are broken down by the body.
* **Urine tests.** People with carcinoid tumors have excess levels of a chemical in their urine that's produced when the body breaks down hormones secreted by carcinoid tumors.
* **Imaging tests.** Imaging tests, including a computerized tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET), X-ray and nuclear medicine scans, may help your doctor pinpoint the carcinoid tumor's location.
* **A scope or camera that sees inside your body.** Your doctor may use a long, thin tube equipped with a lens or camera to examine areas inside your body.  
  An endoscopy, which involves passing a scope down your throat, may help your doctor see inside your gastrointestinal tract. A bronchoscopy, using a scope passed down your throat and into your lungs, can help find lung carcinoid tumors. Passing a scope through your rectum (colonoscopy) can help diagnose rectal carcinoid tumors.  
  To see inside your small intestine, your doctor may recommend a test using a pill-sized camera that you swallow (capsule endoscopy).
* **Removing tissue for laboratory testing.** A sample of tissue from the tumor (biopsy) may be collected to confirm your diagnosis. What type of biopsy you'll undergo depends on where your tumor is located.  
  One way of collecting a tissue sample involves using a needle to draw cells out of the tumor. Another option may be through surgery. The tissue is sent to a laboratory for testing to determine the types of cells in the tumor and how aggressive those cells appear under the microscope.

**Treatment**

Treatment for a carcinoid tumor depends on the tumor's location, whether cancer has spread to other areas of the body, the types of hormones the tumor secretes, your overall health and your own preferences.

Carcinoid tumor treatment options may include:

* **Surgery.** When detected early, a carcinoid tumor may be removed completely using surgery. If carcinoid tumors are advanced when discovered, complete removal may not be possible. In some situations, surgeons may try to remove as much of the tumor as possible, to help control signs and symptoms.
* **Medications to control excess hormones.** Using medications to block hormones secreted by the tumor may reduce the signs and symptoms of carcinoid syndrome and slow tumor growth.  
  Octreotide (Sandostatin, Bynfezia Pen) and lanreotide (Somatuline Depot) are given as injections under the skin. Side effects from either medication may include abdominal pain, bloating and diarrhea. Telotristat (Xermelo) is a pill that is sometimes used in combination with octreotide or lanreotide to further try to improve the symptoms of carcinoid syndrome.
* **Chemotherapy.** Chemotherapy uses strong drugs to kill tumor cells. It can be given through a vein in your arm or taken as a pill. Chemotherapy is sometimes recommended for treating advanced carcinoid tumors that can't be removed with surgery.
* **Targeted drug therapy.** Targeted drug treatments focus on specific abnormalities present within tumor cells. By blocking these abnormalities, targeted drug treatments can cause tumor cells to die. Targeted drug therapy is usually combined with chemotherapy for advanced carcinoid tumors.
* **Drugs that deliver radiation directly to the cancer cells.** Peptide receptor radionuclide therapy (PRRT) combines a drug that seeks out cancer cells with a radioactive substance that kills them. In PRRT for carcinoid tumors, the drug is injected into your body, where it travels to the cancer cells, binds to the cells and delivers the radiation directly to them. This therapy may be an option for people with advanced carcinoid tumors.
* **Treatment for cancer that spreads to the liver.** Carcinoid tumors commonly spread to the liver. Treatments may include surgery to remove part of the liver, blocking blood flow to the liver (hepatic artery embolization), and using heat and cold to kill cancer cells. Radiofrequency ablation delivers heat treatments that cause carcinoid tumor cells in the liver to die. Cryoablation uses cycles of freezing and thawing to kill cancer cells.

## **Prevention**

The exact causes for the development of carcinoid tumors remain unclear. Most develop sporadically. As a result, strategies to prevent the development of carcinoid tumours are not yet known. However, certain genetic and medical conditions are known to increase the risk of development. These conditions include multiple endocrine neoplasia, Von Hippel-Lindau syndrome, neurofibromatosis type 1 and tuberous sclerosis. Conditions that affect stomach acid, such as atrophic gastritis, pernicious anemia and Zollinger-Ellison syndrome, may also increase risk.

## **Managing Carcinoid Tumor**

In addition to following all of your clinical team’s instructions, taking your medicines and keeping your appointments, you can help manage carcinoid tumor by learning as much as you can about the disease and taking an active role in your treatment. Here are some other suggestions:

* Follow a nutritious, high-protein diet.
* Avoid alcohol and foods that trigger carcinoid symptoms.
* Avoid stress as much as possible.
* Ask your doctor about the medicines you take. Some, such as decongestants, asthma inhalers and antidepressants, may trigger or make carcinoid symptoms worse.
* Join a support group to learn more about carcinoid tumors and share your feelings with others.
* Try mind-body exercises like yoga or tai chi to help reduce anxiety and stress.
* Try other ways of managing emotional stress: guided imagery, meditation, music therapy and journaling.
* Before appointments, write down your questions and bring them with you. For support during your appointments, bring a family member or close friend.

## Home Remedies

Home remedies will not cure carcinoid tumors. Vitamin supplements may be helpful. Mineral supplements, such as potassium, magnesium and calcium, may also help. Freshly ground nutmeg will sometimes help control diarrhea. Always let your doctor know about any home remedies you want to try.

**DIFFERENTIAL DIAGNOSIS**

Carcinoid syndrome tends to present with varying clinical features, which accounts for the wide range of its differential diagnoses.Some essential differential diagnoses that should be considered while establishing a diagnosis of carcinoid syndrome include the following:

* Irritable bowel syndrome
* Gastrointestinal motility disorders
* Celiac disease
* Anaphylaxis
* Acute urticaria
* Angioedema
* Ogilvie syndrome

**EPIDEMIOLOGY**

Neuroendocrine tumors are relatively rare, but their incidence and prevalence have increased, likely due to improved diagnostic techniques and greater clinical awareness. The annual incidence of neuroendocrine tumors is estimated to be approximately 6.98 cases per 100,000 individuals, with a prevalence of approximately 35 cases per 100,000 individuals in the United States. These tumors can affect individuals of all racial and ethnic backgrounds, although some studies suggest a slightly higher prevalence among Caucasians. Neuroendocrine tumors are generally more common in females than males, depending on the primary tumor site. For instance, a female predominance is observed in pancreatic and gastrointestinal neuroendocrine tumors. However, the gender distribution can vary across anatomical sites and tumor types. The peak age for diagnosis typically falls between the fifth and seventh decades of life

## **Genetic Findings:**

* MEN1 gene mutations:
  + The most common genetic alteration associated with carcinoid tumors, especially in familial cases linked to Multiple Endocrine Neoplasia type 1 (MEN1) syndrome.
  + MEN1 is a tumor suppressor gene located on chromosome 11q13. Loss of heterozygosity (LOH) at chromosome 11, including MEN1 region, is frequent in sporadic carcinoid tumors (~58-78% show LOH in studies).
  + MEN1 mutations lead to loss of menin protein function, disrupting cell cycle regulation.
* Other inherited gene mutations:
  + Less commonly, carcinoid tumors may be associated with inherited mutations in:
    - NF1 (Neurofibromatosis type 1 gene)
    - VHL (Von Hippel-Lindau gene)
    - TSC1/TSC2 (Tuberous sclerosis complex genes)
* Sporadic mutations and genomic instability:
  + Most carcinoid tumors arise from sporadic mutations occurring after birth.
  + Genetic analyses reveal genomic instability and LOH patterns involving tumor suppressor genes on chromosome 11 and DNA mismatch repair gene mutations.
  + Unlike many other cancers, mutations in common oncogenes like *KRAS* and *p53* are rare or absent in carcinoid tumors.
* Rare or novel mutations:
  + Some familial carcinoid cases have been linked to mutations in the IPMK gene, though this is uncommon and not found in sporadic tumors.
  + Whole exome sequencing studies show genetic heterogeneity with few recurrent somatic mutations beyond MEN1.
* Lack of BRAF mutations:
  + Unlike some other neuroendocrine tumors, carcinoid tumors generally do not harbor *BRAF* mutations.

**Doctor-patient conversation about carcinoid tumors**,:

Doctor: "Your tests have shown that you have a carcinoid tumor, which is a type of neuroendocrine tumor. These tumors arise from hormone-producing cells and can be found in various parts of the body, most commonly in the gastrointestinal tract or lungs."

Patient: "What does this mean for me? Is it cancer?"

Doctor: "Carcinoid tumors are a form of cancer, but they tend to grow more slowly than many other types. Some carcinoid tumors produce hormones that can cause symptoms like flushing, diarrhea, or wheezing, known as carcinoid syndrome. Others may not cause symptoms until they grow larger or spread."

Patient: "What are my treatment options?"

Doctor: "Treatment depends on the tumor’s size, location, whether it has spread, and if it’s causing symptoms. Options include surgery to remove the tumor if it’s localized, medications called somatostatin analogues to control hormone-related symptoms, targeted therapies, and sometimes chemotherapy or peptide receptor radionuclide therapy for advanced cases."

Patient: "What side effects should I expect?"

Doctor: "Side effects vary by treatment. Surgery risks include typical surgical complications. Medications like somatostatin analogues can cause gastrointestinal upset or gallstones. Chemotherapy and other systemic treatments have their own side effects, which we will discuss in detail if those are recommended."

Patient: "Will the treatment cure me?"

Doctor: "If the tumor is caught early and completely removed, surgery can be curative. However, carcinoid tumors can sometimes come back or spread, so ongoing monitoring is important. For advanced disease, treatments focus on controlling symptoms and slowing tumor growth."

Patient: "How often will I need follow-up?"

Doctor: "Typically, we schedule regular follow-ups every 3 to 6 months initially, including imaging and blood tests, to monitor your condition and adjust treatment as needed."

Patient: "Are there support groups or resources you recommend?"

Doctor: "Yes, there are several organizations like the Carcinoid Cancer Foundation and Neuroendocrine Tumor Research Foundation that offer support, education, and connect patients with others facing similar diagnoses. I’ll provide you with their information."

Patient: "What if I want a second opinion?"

Doctor: "That’s a good idea, especially for rare tumors like carcinoid. I can help you find specialists experienced in neuroendocrine tumors."

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### **Salivary gland cancer**

“Salivary gland cancer” is a term used to describe malignant tumors that affect your salivary glands. Your salivary glands are located in your mouth and throat. They produce saliva — or spit — that helps your digestive system begin breaking down food.

Salivary gland tumors may be benign (noncancerous) or malignant (cancerous). Both types may affect any of your salivary glands.

Salivary cancer is rare. Only 1% of tumors affecting the head and neck are salivary cancer. The most common types of salivary gland cancer are mucoepidermoid carcinoma and adenoid cystic carcinoma. Together, they make up half of all malignant salivary gland tumors.

#### **Who is likely to have salivary gland cancer?**

Anyone can develop salivary gland cancer, but men are more likely to have malignant salivary gland tumors. You’re also more likely to develop cancer in a salivary gland if you:

* Are 55 or older.
* Smoke or use alcohol frequently.
* Have received radiation therapy to your head or neck.
* Work in certain occupations, including plumbing, rubber products manufacturing, asbestos mining and leatherwork.

Studies have shown that some rare types of salivary gland cancer may occur more commonly in people with certain viral infections, like Epstein-Barr virus and human papillomavirus (HPV). Still, these infections don’t cause salivary gland cancer. More research is needed to understand the connection.

## **Symptoms and Causes**

Salivary gland cancer tends to start in the three major salivary glands.

### **What causes salivary gland cancer?**

The exact cause of most salivary gland cancers is unknown. Salivary gland tumors can occur in any salivary gland located in or near your mouth. Most commonly, tumors occur in the three major salivary glands. These include your:

* Parotid glands (inside each cheek).
* Submandibular glands (below your jawbone).
* Sublingual glands (along the floor of your mouth).

Most salivary gland tumors — both malignant and benign — start in your parotid glands.

Salivary gland cancer also occurs within the microscopic minor salivary glands. These glands are within the roof or floor of your mouth, the lining of your tongue and lips, and the inside of your cheeks, sinuses, nose and voice box. Tumors rarely form in minor salivary glands, but most that do are malignant.

Left untreated, pieces of these tumors can break away and spread to other parts of your body through your bloodstream or lymphatic system (metastasize). Cancer that’s metastasized is more challenging to treat than cancer that stays in your salivary gland. Salivary gland cancers can metastasize to your lungs, bone and liver.

### **Symptoms of salivary gland cancer**

A small number of people with salivary gland cancer don’t have symptoms. In most cases, salivary gland cancer causes a painless lump on a salivary gland.

If you have a malignant salivary gland tumor, you’re more likely to experience other symptoms, including:

* Weakness or numbness in your face, neck, jaw or mouth.
* Persistent pain in your face, neck, jaw or mouth.
* Difficulty opening your mouth fully or moving your facial muscles.
* Trouble swallowing.
* Bleeding from your mouth.

## **Diagnosis and Tests**

Your healthcare provider diagnoses salivary gland cancer with a physical examination and a review of your medical and personal history. They’ll check for lumps in your salivary glands and see how your facial nerves respond to stimulation. They’ll ask about your symptoms and previous cancer diagnoses.

Your provider may order additional tests to confirm the presence of a tumor or cancer cells. These tests may include:

* CT scan: A CT scan uses X-rays to provide images of masses within salivary glands. It can provide information on a tumor’s size and show if the cancer’s spread to other parts of your body, like your lungs or bone tissue.
* Magnetic resonance imaging (MRI): An MRI uses magnets and radio waves to create pictures of internal body structures. Like a CT scan, an MRI scan can provide information on a tumor’s size. An MRI is especially good at showing if cancer’s spread to soft tissue, like muscles, blood vessels and nerves.
* Positron emission tomography (PET) scan: A PET scan uses small amounts of radioactive materials to see if cancer has spread to your lymph nodes or elsewhere in your body. You may receive a PET scan and a CT scan simultaneously (a PET-CT).
* Biopsy: A biopsy collects a small tissue and fluid sample from a salivary gland tumor. A medical specialist called a pathologist examines the sample in a lab for signs of cancer cells. To collect the sample, your provider may perform a fine-needle aspiration or a core needle biopsy.

A biopsy is the only way to confirm that a salivary gland tumor is cancerous.

### **How is salivary gland cancer staged?**

Your healthcare provider will stage your cancer as part of your diagnosis. Cancer staging provides information about your tumor that can help guide treatment.

The staging system used for tumors that form in your parotid glands, submandibular glands and sublingual glands follows the TLM system:

* T: Tumor size and location.
* L: Whether the cancer has spread to your lymph nodes.
* M: Whether the cancer has metastasized, or spread to organs.

A different system is used to stage cancers that form in minor salivary glands.

Understanding your cancer stage is important to understanding both your treatment options and likely outcomes. Ask your provider to explain your cancer stage and what this means for your diagnosis.

## **Management and Treatment**

Surgery is usually the best treatment option for tumors that can be safely removed. If a tumor is growing fast or if it’s spread to other parts of your body, your healthcare provider may recommend additional treatments.

Treatments include:

* Surgery: Surgery is the primary treatment for malignant salivary gland tumors. In addition to removing the tumor, your provider may remove your lymph nodes (lymphadenectomy) if they suspect the cancer’s spread there. After surgery, you’ll likely receive radiation therapy to kill any remaining cancer cells, so the cancer doesn’t return.
* Radiation therapy: Radiation therapy uses a machine that directs radiation toward the part of your body with cancer cells, destroying them. Photon-beam and neutron beam radiation therapy are two types of radiation therapy used to treat salivary gland cancer. You may also receive radiation as a part of palliative care. Palliative care provides symptom relief and can improve your quality of life.
* Chemotherapy: Chemotherapy uses drugs to destroy cancer cells. You may receive chemotherapy if your cancer has spread from your salivary glands to other tissues outside of your head and neck.

Your healthcare provider may recommend that you participate in a clinical trial. A clinical trial is research that studies the safety and effectiveness of new treatments. These treatments include:

* Immunotherapy: Immunotherapy uses drugs to help your immune system identify cancer cells and fight them. Researchers are studying the role of a specific type of immunotherapy called checkpoint inhibitors in fighting metastasized cancer.
* Targeted therapy: Targeted therapy uses drugs that target weaknesses in a cancer cell’s genetic code (DNA) to destroy the cancer or stop it from growing. Researchers are studying the effectiveness of targeted therapies in people with adenoid cystic carcinomas that have metastasized.
* Radiosensitizers: Radiosensitizers are drugs that make cancer cells more sensitive to radiation. Research is ongoing into how radiosensitizers and radiation therapy can help with salivary gland cancer treatment.

Depending on your cancer, you may receive a combination of treatments to remove the cancer and prevent it from growing back (recurring).

### **What complications are associated with benign salivary gland tumors?**

Benign salivary gland tumors may become malignant over time. The symptoms of salivary gland cancers include rapid enlargement of a pre-existing mass in or around your mouth, numbness, weakness and facial pain. These symptoms may interfere with your ability to speak and swallow properly.

## **Outlook / Prognosis**

Most people recover fully from salivary gland tumor treatment if the cancer is diagnosed and treated early. Your prognosis will depend on factors like:

* The tumor’s size.
* Whether the cancer’s spread.
* Whether the cancer has recurred.
* Which salivary gland contains the cancer cells.
* How abnormal the cancer cells appear when viewed with a microscope.
* Your overall health status.

### **Survival rate of salivary gland cancer**

Cancer survival rates reflect research that tracks how many people with a particular cancer diagnosis are alive over a period of time, usually five years. With salivary gland cancer, survival rates depend on the type of cancer. For example, the survival rate for mucoepidermoid carcinoma ranges from 75% to 90% at five years. The location of the tumor matters, too. If it’s only in your salivary gland, the survival rate is 94%. The survival rate is lower if the cancer’s spread.

It’s important to keep in mind that this data doesn’t consider factors unique to you — like your health, your response to treatment, etc.

Ask your healthcare provider about your likely outcomes based on your unique situation.

## **Prevention**

There’s no way to prevent salivary gland cancer. You can reduce your overall cancer risk by avoiding certain risk factors, like smoking and drinking too much alcohol.

### **When should I call my doctor?**

If you have any symptoms of a salivary gland tumor, especially if your symptoms last for more than two weeks, make an appointment with a healthcare provider.

## **Differential Diagnoses of Salivary Gland Lesions**

## 1. Benign Salivary Gland Tumors

* Pleomorphic adenoma: Most common benign tumor, especially in the parotid gland (~50%).
* Warthin tumor: Almost exclusively in the parotid, often bilateral in older males.
* Myoepithelioma: Considered a subtype of pleomorphic adenoma.
* Basal cell adenoma

## 2. Malignant Salivary Gland Tumors

* Mucoepidermoid carcinoma: Most common malignant salivary tumor.
* Adenoid cystic carcinoma: Characterized by perineural invasion.
* Salivary duct carcinoma: Aggressive tumor, often androgen receptor positive.
* Carcinoma ex pleomorphic adenoma: Malignant transformation of a benign pleomorphic adenoma.
* Lymphoepithelial carcinoma
* Acinic cell carcinoma
* Carcinosarcoma (true mixed tumor)

## 3. Non-neoplastic and Other Conditions Mimicking Tumors

* Salivary cysts and branchial cleft cysts
* Sialolithiasis (salivary gland stones) causing obstruction and swelling
* Chronic sialadenitis (inflammation)
* Sjogren’s syndrome (autoimmune infiltration causing gland enlargement)
* Sarcoid infiltration (Heerfordt’s syndrome)
* Lymphoepithelial cysts
* Lymphoma: Primary MALT lymphoma or secondary involvement of intraparotid nodes
* Metastases: From cutaneous squamous cell carcinoma, melanoma, or other primaries to intraparotid lymph nodes
* Regional lymphadenopathy from infections or malignancies
* Intraparotid facial nerve schwannoma
* Bell’s palsy (facial nerve palsy mimicking tumor symptoms)

**EPIDEMIOLOGY**

Salivary gland cancers are not very common, making up 6% to 8% of all head and neck cancers in the United States. There are about 2,000 to 2,500 cases in the US each year. They occur at a rate of about 3 cases per 100,000 people per year in the Western world.

These cancers can occur in people of almost any age, but they become more common as people get older. The average age of people when they are diagnosed is 55.

Most salivary gland cancers are found in the parotid glands, followed by the submandibular, sublingual, and minor salivary glands.

## **Genetic Alterations and Pathways**

* TP53 mutations:
  + The most common mutation across various salivary gland tumors, found in approximately 30.8% of cases.
  + TP53 is a tumor suppressor gene that regulates cell cycle and apoptosis; its mutation leads to uncontrolled cell growth.
* Cyclin pathway genes:
  + Alterations in CCND1, CDK4/6, CDKN2A/B occur in about 26.5% of tumors.
  + These genes regulate cell cycle progression, and their dysregulation promotes tumor proliferation.
* PI3K pathway mutations:
  + Involving genes like PIK3CA, PIK3R1, PTEN, AKT1/3, seen in about 23.9% of cases.
  + This pathway controls cell growth and survival, and mutations activate oncogenic signaling.
* NOTCH1 mutations:
  + Affect cell differentiation and proliferation, contributing to tumor development.
* Gene fusions:
  + Specific translocations are characteristic of certain tumor types:
    - ETV6-NTRK3 fusion in secretory carcinoma (a salivary gland tumor subtype).
    - CRTC1-MAML2 fusion in mucoepidermoid carcinoma, associated with MYC oncogene activation.
  + These fusions serve as diagnostic and prognostic biomarkers.
* Other mutations:
  + Alterations in EGFR, PDGFRA, HRAS, MDM2, ERBB2 have been reported in subsets of tumors.
  + These may represent potential therapeutic targets.

## Molecular Landscape Highlights

* Each patient’s tumor often harbors a unique combination of mutations, with only a small percentage sharing identical molecular profiles.
* Significant co-occurrences include TP53 with ERBB2, cyclin pathway mutations with MDM2, and PI3K pathway mutations with HRAS.

**Salivary Gland Procedures and Typical Treatment Timeline**

## 1. Initial Evaluation and Diagnosis

* Clinical examination, imaging (MRI, CT, ultrasound), and fine needle aspiration cytology (FNAC) or biopsy to confirm diagnosis and tumor type.
* Multidisciplinary team planning involving head and neck surgeons, radiologists, oncologists.

## 2. Surgery

* Primary treatment for most salivary gland tumors, especially if localized and operable.
* Types of surgery:
  + Parotidectomy (partial or total removal of the parotid gland).
  + Submandibular gland excision or minor salivary gland tumor resection.
  + Possible removal of involved lymph nodes (neck dissection) if cancer spread is suspected.
* Surgery aims to remove the tumor with clear margins while preserving facial nerve function if possible.
* Recovery:
  + Hospital stay typically 1–3 days.
  + Initial recovery takes about 2 weeks; full recovery (including facial nerve function) may take months to a year.
  + Surgical drains usually removed within 1–2 weeks.
  + Facial nerve function assessed immediately post-op and during follow-ups.

## 3. Adjuvant Therapy

* Radiation therapy is commonly given after surgery if:
  + The tumor is high-grade or incompletely resected.
  + There is perineural invasion or lymph node involvement.
  + Certain tumor types like adenoid cystic carcinoma.
* Radiation typically starts 4–6 weeks after surgery once healing is adequate.
* Treatment duration: usually 5–7 weeks of daily sessions (Monday to Friday).
* Special radiation techniques (fast-neutron or photon-beam) may be used depending on tumor type.

## 4. Chemotherapy and Targeted Therapy

* Chemotherapy is generally reserved for advanced, metastatic, or unresectable tumors and is often palliative.
* Targeted therapies or immunotherapy may be options in clinical trials or specific molecular subtypes.
* Chemotherapy may be combined with radiation in select cases.

## 5. Follow-up and Surveillance

* Regular follow-up is crucial due to risk of recurrence or late complications.
* Typical follow-up schedule after treatment:

**doctor-patient conversation about salivary gland tumors**,

Doctor: "You have a growth in your salivary gland. These growths can be either benign or malignant, so we need to carefully evaluate it to understand what it is."

Patient: "Does that mean I have cancer?"

Doctor: "Not necessarily. Many salivary gland tumors are benign, like pleomorphic adenomas or Warthin tumors, which are non-cancerous and often slow growing. However, some can be malignant, meaning cancerous, so we need further tests to be sure."

Patient: "What tests will I need?"

Doctor: "We usually start with imaging, like an ultrasound or MRI, to see the size and location of the tumor. Then, we often do a fine needle aspiration biopsy, which uses a thin needle to take a small sample of cells for analysis. This helps us determine if the tumor is benign or malignant."

Patient: "If it’s cancer, what are my treatment options?"

Doctor: "Surgery is the main treatment for most salivary gland tumors. The goal is to remove the tumor completely while preserving important structures like the facial nerve. Depending on the tumor type and stage, you may also need radiation therapy after surgery. Chemotherapy is less common but may be used in advanced cases."

Patient: "What are the risks or side effects of treatment?"

Doctor: "Surgery can carry risks such as facial nerve weakness, numbness, or dry mouth, but we take great care to minimize these. Radiation therapy can cause skin changes, dry mouth, or difficulty swallowing. We will support you throughout treatment to manage any side effects."

Patient: "Will the treatment cure me?"

Doctor: "Many patients with benign tumors are cured by surgery alone. For malignant tumors, the prognosis depends on the type and stage, but early detection and treatment improve outcomes significantly."

Patient: "How often will I need follow-up?"

Doctor: "You’ll have regular follow-up visits, especially in the first few years after treatment, to monitor for any recurrence or complications. The schedule usually starts with visits every few months, gradually extending to yearly visits if all goes well."

Patient: "Are there support groups or resources you recommend?"

Doctor: "Yes, there are patient support groups and educational resources available through cancer centers and organizations like the Head and Neck Cancer Alliance. I can provide you with contact information and materials to help you connect with others and learn more.

REFERENCES

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[Salivary Gland Cancer: Symptoms, Causes & Treatment](https://my.clevelandclinic.org/health/diseases/17965-salivary-gland-cancer#overview)

**AIDS RELATED LYMPHOMA**

AIDS-related lymphoma is a disease in which cancer or malignant cells are found in the lymph systems of patients who have AIDS.

The lymph system is made up of thin tubes that branch, like blood vessels, into all parts of the body. Lymph vessels carry lymph, a colorless, watery fluid that contains white blood cells called lymphocytes. Along the network of vessels are groups of small, bean-shaped organs called lymph nodes. Clusters of lymph nodes make and store infection-fighting cells. The spleen, an organ in the upper abdomen that makes lymphocytes and filters old blood cells from the blood; the thymus, a small organ beneath the breastbone; and the tonsils, an organ in the throat, are part of the lymph system.

Because there is lymph tissue in many parts of the body, the cancer can spread to almost any of the body's organs or tissues including the liver, bone marrow (spongy tissue inside the large bones of the body that makes blood cells), spleen or brain.

### Types of lymphoma

Lymphomas are divided into two general types, Hodgkin's lymphoma and non-Hodgkin's lymphomas, which are classified by the way their cells look under a microscope. This determination is called the histology. Histology also is used to determine the subtype of non-Hodgkin's lymphoma.

The types of non-Hodgkin's lymphomas are classified by how quickly they spread: low-grade, intermediate-grade or high-grade. The intermediate or high-grade lymphomas grow and spread faster than the low-grade lymphomas.

Both major types of lymphoma — Hodgkin's lymphoma and non-Hodgkin's lymphoma, especially the more aggressive, intermediate and high grade lymphomas — may occur in adult and pediatric AIDS patients.

A separate type of lymphoma, called primary central nervous system lymphoma, starts in the brain or spinal cord, both of which are part of the central nervous system (CNS). This type of lymphoma is called a "primary CNS lymphoma" because it starts in the central nervous system rather than starting somewhere else in the body and spreading to the CNS. The immune deficiency usually is quite advanced before this develops.

## **Signs & symptoms**

See a doctor if any of the following symptoms persist for longer than two weeks:

* Painless swelling in the lymph nodes in the neck, underarm or groin
* Fever
* Night sweats
* Tiredness
* Weight loss without dieting
* Itchy skin

## **Diagnosis**

If you have AIDS and symptoms of lymphoma, a doctor will carefully check for swelling or lumps in the neck, underarms and groin. Scans may be done to examine lymph nodes inside the body. If the lymph nodes don't feel or look normal, your doctor may need to cut out a small piece of tissue and look at it under the microscope to detect cancer cells. This procedure is called a biopsy.

Once AIDS-related lymphoma is found, more tests will be done to find out if the cancer has spread from where it started to other parts of the body, a process called staging.

## **Treatments**

In general, patients with AIDS-related lymphoma respond to treatment differently from patients with lymphoma who do not have AIDS. AIDS-related lymphoma usually grows faster and spreads outside the lymph nodes and to other parts of the body more often than lymphoma that is not related to AIDS.

Because therapy can damage weak immune systems even further, patients who have AIDS-related lymphoma may be treated with lower doses of drugs than those who do not have AIDS.

There are different types of treatment for patients with AIDS-related lymphoma.

Treatment of AIDS-related lymphoma combines treatment of the lymphoma with treatment for AIDS.

The following types of treatment are used:

* + Chemotherapy
  + Radiation therapy
  + High-dose chemotherapy with stem cell transplant
  + Targeted therapy

New types of treatment are being tested in clinical trials.

Treatment for AIDS-related lymphoma 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 tests may be needed.

### **There are different types of treatment for patients with AIDS-related lymphoma.**

Different types of treatment are available for patients with [AIDS-related](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=444964&version=patient&language=English&dictionary=Cancer.gov) lymphoma. 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](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45333&version=patient&language=English&dictionary=Cancer.gov). 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.

### **Treatment of AIDS-related lymphoma combines treatment of the lymphoma with treatment for AIDS.**

Patients with AIDS have weakened [immune systems](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=46356&version=patient&language=English&dictionary=Cancer.gov) and treatment can cause the immune system to become even weaker. For this reason, treating patients who have AIDS-related lymphoma is difficult and some patients may be treated with lower [doses](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=44664&version=patient&language=English&dictionary=Cancer.gov) of [drugs](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=348921&version=patient&language=English&dictionary=Cancer.gov) than lymphoma patients who do not have AIDS.

Highly active antiretroviral therapy (HAART) is used to lessen the damage to the immune system caused by [HIV](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=44985&version=patient&language=English&dictionary=Cancer.gov). Treatment with HAART may allow some patients with AIDS-related lymphoma to safely receive anticancer drugs in standard or higher doses. In these patients, treatment may work as well as it does in lymphoma patients who do not have AIDS. Medicine to prevent and treat infections, which can be serious, is also used.

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

#### **Chemotherapy**

Chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer [cells](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=46476&version=patient&language=English&dictionary=Cancer.gov), either by killing the cells or by stopping them 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). When chemotherapy is placed directly into the cerebrospinal fluid (intrathecal chemotherapy), an organ, or a body [cavity](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=463703&version=patient&language=English&dictionary=Cancer.gov) such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy). Combination chemotherapy is treatment using more than one anticancer drug.

Intrathecal chemotherapy may be used in patients who are more likely to have lymphoma in the [central nervous system](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=46481&version=patient&language=English&dictionary=Cancer.gov) (CNS).

Chemotherapy is used in the treatment of AIDS-related peripheral/[systemic](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45921&version=patient&language=English&dictionary=Cancer.gov) lymphoma. It is not yet known whether it is best to give HAART at the same time as chemotherapy or after chemotherapy ends.

[Colony-stimulating factors](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45649&version=patient&language=English&dictionary=Cancer.gov) are sometimes given together with chemotherapy. This helps lessen the [side effects](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=46580&version=patient&language=English&dictionary=Cancer.gov) chemotherapy may have on the bone marrow.

#### **Radiation therapy**

Radiation therapy is a cancer treatment that uses high-energy [x-rays](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45944&version=patient&language=English&dictionary=Cancer.gov) 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.

#### **High-dose chemotherapy with stem cell transplant**

High doses of chemotherapy are given to kill cancer cells. Healthy cells, including [blood](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=270735&version=patient&language=English&dictionary=Cancer.gov)-forming cells, are also destroyed by the cancer treatment. [Stem cell transplant](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=46695&version=patient&language=English&dictionary=Cancer.gov) is a treatment to replace the blood-forming cells. [Stem cells](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=46598&version=patient&language=English&dictionary=Cancer.gov) (immature blood cells) are removed from the blood or bone marrow of the patient and are frozen and stored. After the patient completes chemotherapy, the stored stem cells are thawed and given back to the patient through an [infusion](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45738&version=patient&language=English&dictionary=Cancer.gov). These reinfused stem cells grow into (and restore) the body's blood cells.

#### **Targeted therapy**

[Targeted therapy](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=270742&version=patient&language=English&dictionary=Cancer.gov) is a type of treatment that uses [drugs](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=348921&version=patient&language=English&dictionary=Cancer.gov) or other substances to identify and attack specific cancer cells. Targeted therapies usually cause less harm to normal cells than chemotherapy or radiation therapy do.

* [Monoclonal antibodies](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=46066&version=patient&language=English&dictionary=Cancer.gov): Monoclonal antibodies are immune system proteins made in the laboratory to treat many diseases, including cancer. As a cancer treatment, these [antibodies](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=44918&version=patient&language=English&dictionary=Cancer.gov) can attach to a specific target on cancer cells or other cells that may help cancer cells grow. The antibodies are able to then kill the cancer cells, block their growth, or keep them from spreading. Monoclonal antibodies are given by infusion. These may be used alone or to carry drugs, [toxins](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=46622&version=patient&language=English&dictionary=Cancer.gov), or radioactive material directly to cancer cells. Rituximab is used in the treatment of AIDS-related peripheral/systemic lymphoma.

### **Patients may want to think about taking part in a clinical trial.**

For some patients, taking part in a clinical trial may be the best treatment choice. Clinical trials are part of the cancer research process. Clinical trials are done to find out if new cancer treatments are safe and effective or better than the [standard treatment](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=44930&version=patient&language=English&dictionary=Cancer.gov).

Many of today's standard treatments for cancer are based on earlier clinical trials. Patients who take part in a clinical trial may receive the standard treatment or be among the first to receive a new treatment.

Patients who take part in clinical trials also help improve the way cancer will be treated in the future. Even when clinical trials do not lead to effective new treatments, they often answer important questions and help move research forward.

**Follow-up tests may be needed.**

As you go through treatment, you will have follow-up tests or check-ups. Some tests that were done to diagnose or [stage](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45885&version=patient&language=English&dictionary=Cancer.gov) the cancer may be repeated to see how well the treatment is working. Decisions about whether to continue, change, or stop treatment may be based on the results of these tests.

Some of the tests will continue to be done from time to time after treatment has ended. The results of these tests can show if your condition has changed or if the cancer has recurred (come back).

## **Treatment of AIDS-Related Peripheral/Systemic Lymphoma**

Treatment of AIDS-related peripheral/systemic lymphoma may include the following:

* Combination chemotherapy with or without targeted therapy.
* [High-dose chemotherapy](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=346522&version=patient&language=English&dictionary=Cancer.gov) and stem cell transplant, for lymphoma that has not responded to treatment or has come back.
* Intrathecal chemotherapy for lymphoma that is likely to spread to the central nervous system (CNS).

## **Treatment of AIDS-Related Primary Central Nervous System Lymphoma**

Treatment of AIDS-related primary central nervous system lymphoma may include the following:

* External radiation therapy.

## **Stages of AIDS-Related Lymphoma**

After AIDS-related lymphoma has been diagnosed, tests are done to find out if cancer cells have spread within the lymph system or to other parts of the body.

There are three ways that cancer spreads in the body.

The following stages are used for AIDS-related lymphoma:

* + Stage I
  + Stage II
  + Stage III
  + Stage IV

For treatment, AIDS-related lymphomas are grouped based on where they started in the body, as follows:

Peripheral/systemic lymphoma

Primary CNS lymphoma

### **After AIDS-related lymphoma has been diagnosed, tests are done to find out if cancer cells have spread within the lymph system or to other parts of the body.**

The process used to find out if cancer [cells](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=46476&version=patient&language=English&dictionary=Cancer.gov) have spread within the [lymph system](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45764&version=patient&language=English&dictionary=Cancer.gov) or to other parts of the body is called staging. The information gathered from the staging process determines the [stage](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45885&version=patient&language=English&dictionary=Cancer.gov) of the disease. It is important to know the stage in order to plan treatment, but AIDS-related lymphoma is usually advanced when it is [diagnosed](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=46450&version=patient&language=English&dictionary=Cancer.gov).

The following tests and procedures may be used to find out if the cancer has spread:

* **MRI (magnetic resonance imaging) with** [**gadolinium**](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=597153&version=patient&language=English&dictionary=Cancer.gov): 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 brain and spinal cord. A substance called gadolinium is injected into the patient through a [vein](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=476471&version=patient&language=English&dictionary=Cancer.gov). The gadolinium collects around the cancer cells so they show up brighter in the picture. This procedure is also called nuclear magnetic resonance imaging (NMRI).
* **Lumbar puncture**: A procedure used to collect cerebrospinal fluid (CSF) from the [spinal column](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=396787&version=patient&language=English&dictionary=Cancer.gov). This is done by placing a needle between two bones in the [spine](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=415914&version=patient&language=English&dictionary=Cancer.gov) and into the CSF around the spinal cord and removing a sample of the fluid. The sample of CSF is checked under a microscope for signs that the cancer has spread to the brain and spinal cord. The sample may also be checked for Epstein-Barr virus. This procedure is also called an LP or spinal tap.

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

Cancer can spread through [tissue](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=46683&version=patient&language=English&dictionary=Cancer.gov), the [lymph system](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45764&version=patient&language=English&dictionary=Cancer.gov), and the [blood](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=270735&version=patient&language=English&dictionary=Cancer.gov):

* 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](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45020&version=patient&language=English&dictionary=Cancer.gov) to other parts of the body.

**Epidemiology of AIDS-Related Lymphoma (ARL):**

* Incidence and Risk:  
  AIDS-related lymphoma (ARL) is a significant cause of morbidity and mortality in people living with HIV (PLWH). The risk of developing non-Hodgkin lymphoma (NHL) in HIV-infected individuals is 23 to over 350 times higher than in the general population. Before the widespread use of combined antiretroviral therapy (cART), the risk was even higher, with some studies reporting a 165-fold increase in NHL risk within three years of AIDS diagnosis.
* Prevalence:  
  Malignant tumors account for more than 28% of HIV-related deaths, and more than 40% of HIV-infected individuals are eventually diagnosed with AIDS-related lymphoma. ARL comprises about 6.5% to 10% of lymphomas in some regional studies.
* Common Subtypes:  
  The most frequent ARL subtype is Diffuse Large B-Cell Lymphoma (DLBCL), accounting for approximately 45-50% of cases. Other common subtypes include Burkitt lymphoma (BL) (30-40%), plasmablastic lymphoma (PBL), primary central nervous system lymphoma (PCNSL), and primary effusion lymphoma (PEL). T-cell lymphomas are rare.
* Clinical Characteristics:  
  ARL tends to present aggressively, often at an advanced stage (60-70%), with extranodal involvement (80%) and systemic “B symptoms” (fever, night sweats, weight loss). It is more common in patients with low CD4+ counts (<100 cells/μL) and high HIV viral loads.
* Demographics:  
  ARL patients are often younger, with median ages around 40-45 years, and predominantly male. It is more frequent in advanced HIV infection and in regions with limited access to cART.
* Impact of cART:  
  The introduction of cART has significantly decreased the incidence of ARL and improved survival, but NHL remains one of the most common AIDS-defining cancers and a leading cause of death among PLWH. The decline in ARL incidence has been less pronounced compared to other HIV-associated malignancies like Kaposi’s sarcoma.
* Geographic Variation:  
  The incidence and subtype distribution of ARL vary by region. For example, Burkitt lymphoma is endemic in some parts of Africa but less common in AIDS-related cases there

**Doctor-patient conversation about AIDS-related lymphoma (ARL)**:

Doctor:  
“Thank you for coming in today. I want to discuss your diagnosis. The tests show you have AIDS-related lymphoma, which is a type of lymphoma that occurs more commonly in people living with HIV. I know this can be overwhelming news, but there are effective treatments available, and we have a team experienced in managing this condition.”

Patient:  
“That sounds scary. What does this mean for me? Can it be treated?”

Doctor:  
“AIDS-related lymphoma is an aggressive cancer, but with modern treatments, many patients respond well. We typically use chemotherapy combined with antiretroviral therapy (ART) to control both the lymphoma and HIV. Your immune system status and viral load will guide how we tailor your treatment.”

Patient:  
“Will the HIV medicines interfere with the cancer treatment?”

Doctor:  
“That’s an important question. Some HIV medications can interact with chemotherapy drugs, so we carefully select your antiretroviral regimen to minimize side effects and drug interactions. In fact, continuing ART during chemotherapy improves outcomes and helps your immune system recover faster.”

Patient:  
“What kind of side effects should I expect?”

Doctor:  
“Side effects depend on the chemotherapy drugs used but can include fatigue, nausea, low blood counts, and increased infection risk. We will monitor you closely and provide supportive care to manage these effects.”

Patient:  
“Is there a special team that will help me?”

Doctor:  
“Yes, you will be cared for by a multidisciplinary team including HIV specialists, oncologists, haematologists, nurses, and pharmacists who coordinate your care. Some centers have joint HIV and lymphoma clinics to provide comprehensive support.”

Patient:  
“How often will I need to come for treatment and check-ups?”

Doctor:  
“Treatment schedules vary but usually involve frequent visits during chemotherapy cycles, often every few weeks. After treatment, regular follow-ups continue to monitor your lymphoma and HIV status.”

Patient:  
“What is my outlook with this diagnosis?”

Doctor:  
“Prognosis depends on factors like lymphoma subtype, stage, your immune function, and overall health. Since the introduction of ART, outcomes have improved significantly. Many patients achieve remission and live longer, healthier lives.”

Patient:  
“Are there support services to help me cope?”

Doctor:  
“Absolutely. We can connect you with counseling, peer support groups, and social services. You won’t have to face this alone.”

Patient:  
“Thank you for explaining everything. I feel more hopeful knowing there’s a plan.”

Doctor:  
“You’re welcome. We’re here to support you every step of the way. Please don’t hesitate to ask questions or share concerns anytime.”

REFERENCES

<https://www.ucsfhealth.org/conditions/aids-related-lymphoma>

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### **Appendix cancer**

Appendix cancer — also called appendiceal cancer — is a rare disease. It occurs when the cells in your appendix mutate (change) and grow out of control.

Your appendix is part of your digestive system. It’s a small tube-like pouch located on the lower right side of your abdomen, near the junction of your large intestine (colon) and small intestine. Scientists don’t know for sure what your appendix does. But some believe it helps your immune system function. Others consider it a vestigial organ (one that’s no longer useful in modern times).

#### **Types of appendix cancer**

There are several benign (noncancerous) and malignant tumors that can develop in your appendix. Malignant, or cancerous ones, have the potential to grow and spread. Experts classify malignant appendix tumors based on the type of cell where the cancer starts. Types include:

* Appendiceal adenocarcinoma.
* Neuroendocrine tumors.

##### **Appendiceal adenocarcinoma (epithelial tumors)**

Most appendix cancers are appendiceal adenocarcinoma. Adenocarcinoma cancers start in the glandular tissue that lines your organs. There are several categories of appendiceal adenocarcinoma, including:

* Mucinous adenocarcinoma. This type starts in the lining of your appendix and releases mucin, a component of mucus. Although these tumors can spread, most don’t spread beyond your abdomen.
* Colonic-type (nonmucinous) adenocarcinoma. These tumors develop near the bottom of your appendix. They behave a lot like colon cancer tumors and cause many of the same symptoms.
* Signet ring cell adenocarcinoma. This variant is rare, but it can occasionally form in your appendix. The cancer cells secrete and store large amounts of mucin. It’s called signet ring adenocarcinoma because the cancer cells have a signet ring appearance under a microscope.
* Goblet cell adenocarcinoma. This extremely rare variant of adenocarcinoma has some features of neuroendocrine tumors, too.

#### **Appendiceal neuroendocrine tumors (carcinoid tumors)**

Neuroendocrine tumors affect neuroendocrine cells, which receive signals from your nervous system and release hormones. In most cases, these tumors grow slowly.

Appendix cancer is extremely rare. In the United States, appendix cancer affects approximately 1 to 2 people out of every 1 million each year. That’s significantly less than even 1% of the population.

## **Symptoms and Causes**

You can have appendix cancer without developing symptoms. Or you may not notice symptoms until the tumor has spread. Appendix cancer symptoms vary from person to person and may include:

* Appendicitis (inflammation or infection of your appendix).
* Bloating (fullness or tightness in your belly).
* Fluid buildup in your abdomen (ascites).
* Increase in waist size.
* Pain in your abdomen or pelvis.
* Changes in bowel habits (including diarrhea).
* Nausea and vomiting.
* Feeling full soon after you start eating (early satiety).

Sometimes, appendix cancer occurs alongside a rare condition called pseudomyxoma peritonei (PMP). With PMP, cancer cells secrete jelly-like mucin that can cause your appendix to swell. Over time, it can cause symptoms like a bloated stomach and abdominal pain.

### **What causes appendix cancer?**

Appendix cancer starts when the cells in your appendix mutate and grow out of control. But experts don’t know what sets this process in motion.

#### **Risk factors**

Certain factors may increase your risk of appendix cancer, including:

* Age. Appendix cancer can occur at any age, but it’s more likely to develop in people between 40 and 60. Most people diagnosed are in their 50s.
* Sex. Females are more likely to develop neuroendocrine tumors in their appendix.
* Smoking or using tobacco products. Tobacco use can increase your chances of all cancers, including appendix cancer.
* Medical history. Certain health conditions, including atrophic gastritis, pernicious anemia and Zollinger-Ellison syndrome, may increase your risk for appendix cancer.
* Family history of cancer. A recent study suggests that some people with appendix cancer inherit genes that increase their cancer risk. But more research is needed to know if some forms might be hereditary (run in families).

## **Diagnosis and Tests**

People with appendix cancer often see their healthcare providers because they’re having symptoms of appendicitis. Diagnosis usually happens after an appendectomy (removal of the appendix). Sometimes, existing tumors show up on imaging tests or surgery for an unrelated condition.

If your provider suspects appendix cancer, they’ll recommend more tests, which may include:

* Imaging tests. Your provider may recommend a computed tomography (CT) scan or MRI (magnetic resonance imaging). These tests take pictures of the tissues inside your body. They can show tumors and reveal signs of cancer spread. When it spreads, appendix cancer advances to nearby abdominal organs or the tissue lining them (peritoneum).
* Laparoscopy. Your provider inserts a laparoscope — a long, slender fiber optic instrument — through an incision (cut) in your abdomen. A small camera captures images of your appendix and projects them onto a screen.
* Biopsy. During this procedure, your provider takes a tissue sample and sends it to a pathology lab to test for cancer cells. It can be difficult to take a biopsy of the appendix. So, if the cancer has potentially spread to another region, your provider will take a sample from that area.
* Blood tests. If your biopsy results are positive for appendix cancer, then your provider will recommend lab tests to check your protein levels. Specific protein levels can help determine how advanced the cancer is.

#### **Stages of appendix cancer**

Cancer staging allows healthcare providers to determine how advanced cancer is, develop the best treatment plan and determine likely treatment outcomes.

Providers use different staging guidelines based on the type of tumor:

* Appendiceal adenocarcinomas: Providers use the TNM staging system. They consider how large tumors are (T), if the cancer has spread to your lymph nodes (N) and if it’s spread to distant organs (M). Cancer that has spread is called metastatic cancer. Providers consider these factors together to assign a stage from one to four, with one being early-stage cancer and four being advanced.
* Appendiceal neuroendocrine tumors: Providers stage neuroendocrine tumors based on whether surgery can remove them completely. They also consider the tumor grade (how abnormal the cells look beneath a microscope). Your prognosis is better if you have a low-grade tumor (few abnormal cells) that a provider can remove with surgery.

Staging is especially complex in appendix cancer because there are so many different types of tumors. Each type has different characteristics that will shape your treatment options and prognosis.

But don’t be intimidated. Ask your healthcare provider to explain what your cancer type and stage mean for you.

## **Management and Treatment**

There are several potential appendix cancer treatments, including surgery and drug treatments. Your healthcare provider will consider several things before planning your treatment, including the size and stage of the tumor, your overall health and your personal preferences.

#### **Surgery**

Surgery is the most common treatment for appendix cancer. Surgical approaches include:

* Appendectomy. Removing your appendix may be enough to treat small tumors less than 1 or 2 centimeters (less than an inch).
* Hemicolectomy. You may need additional surgery, like hemicolectomy, for larger and more aggressive tumors. It involves removing part of your large intestine and some lymph nodes in addition to removing your appendix.
* Cytoreductive (debulking) surgery. You may need more extensive surgery for cancer that has spread throughout your abdomen. Your surgeon will remove as much of the tumor as possible, including parts of affected organs.

#### **Drug treatments**

You may need drug treatments for appendix cancer if surgery can’t get rid of all the cancer. Treatments include:

* Chemotherapy. This treatment uses drugs to kill cancer cells that have spread beyond your appendix. It also destroys any cancer cells that may remain after surgery. You can receive the medicine through an injection or by taking a pill.
* Hyperthermic intraperitoneal chemotherapy (HIPEC). HIPEC is a special type of chemotherapy treatment that usually happens during surgery. It involves heating chemotherapy drugs and circulating them inside your abdominal cavity. The heat and direct application make the chemo more powerful and effective.
* Targeted drug therapy. The goal of this treatment is to target cancer cells while limiting damage to healthy cells. Specific drugs target certain genes or proteins that encourage cancer growth. Drugs providers use in targeted therapy for appendix cancer include cetuximab, bevacizumab, ramucirumab and panitumumab.

## **Outlook / Prognosis**

Your experience depends on many things, like the type of tumor, its size and its grade. Your overall health and how you respond to treatment are important, too.

Some types of appendix cancer are curable. For example, most low-grade appendiceal neuroendocrine tumors are curable with surgery. Generally, the smaller the tumor, the more likely it is that treatment will get rid of the cancer for good. Larger tumors typically spread quickly and may not respond as well to treatment.

Your healthcare provider can offer guidance on what to expect based on your diagnosis.

#### **Survival rate of appendix cancer**

The five-year survival rate for low-grade appendix cancer is 67% to 97%. That means that 67% to 97% of people diagnosed with the disease are still alive five years later. The five-year survival rate for aggressive tumors or late-stage appendix cancer can be much lower.

Remember that survival rates can’t tell you how you’ll respond to treatment or how long you’ll live. These numbers represent the experiences of people who’ve been diagnosed with appendix cancer in the past. Because appendix cancer is so rare, information about life expectancy may not be precise. If you have questions about survival rates, talk to your healthcare provider.

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

Call your provider immediately if you develop appendix cancer symptoms, including appendicitis, bloating or abdominal pain.

If you already have an appendix cancer diagnosis, call your provider if your symptoms change or worsen. Let them know if you’re experiencing treatment side effects. They can recommend ways to ease your discomfort. They may also connect you with palliative care resources. Palliative care professionals help people with various illnesses (including non-life-threatening ones) manage symptoms.

**EPIDEMIOLOGY**

Cancer of the appendix is observed in less than 2% of appendiceal specimens. There has been a steady rise in the number of appendectomies performed in the United States, as well as the incidence of appendiceal cancer.Gastroenteropancreatic neuroendocrine tumors ( GEP-NETs) account for the most common malignancy of the appendix.Although appendiceal adenocarcinoma is more frequently found amongst men in their 6 to 7 decade of life, in recent decades, there has been a decrease in the age at diagnosis. An increased association with colonic neoplasia and chronic ulcerative colitis has been noted.The appendix is the third most common site for neuroendocrine tumors after the rectum. At the time of diagnosis, over a third of cases are metastatic

**Differential diagnosis (DDX) of appendix cancer**

Benign appendix lesions:

* + *Appendiceal mucocele* (a cystic dilation of the appendix often due to mucin accumulation)
  + *Acute appendicitis* (inflammation of the appendix, often the initial presentation leading to incidental cancer diagnosis)
* Colorectal cancers:  
  Tumors arising from the cecum or colon that may extend into or mimic appendix tumors.
* Adenexal masses (ovarian tumors):  
  Pelvic masses from the ovaries or fallopian tubes can be confused with appendiceal tumors on imaging.
* Carcinoid tumors (neuroendocrine tumors):  
  The most common type of appendix cancer, which must be distinguished from other neuroendocrine tumors elsewhere in the body.
* Other appendix tumors:
  + *Adenocarcinomas* (colonic-type, mucinous, goblet cell adenocarcinoma)
  + *Neuroendocrine carcinomas*
  + *Mixed tumors* containing both adenocarcinoma and neuroendocrine elements
* Pseudomyxoma peritonei:  
  A clinical syndrome often caused by mucinous adenocarcinoma of the appendix, but can also be caused by other mucinous tumors.
* Other abdominal or pelvic masses:  
  Conditions such as abscesses, lymphangiomas, or inflammatory masses can mimic appendiceal cancer.

**Appendix Cancer Treatment: Drug Information and Side Effects**

## Chemotherapy Types for Appendix Cancer

1. Systemic Chemotherapy
   * Delivered intravenously (IV) or orally.
   * Used for stage 4 cancer that has spread beyond the abdomen or after surgery to reduce recurrence risk.
   * Common drugs include combinations used for colorectal-type adenocarcinomas, such as:
     + Fluorouracil (5-FU)
     + Leucovorin (enhances 5-FU)
     + Oxaliplatin
     + Irinotecan
     + Targeted agents may be considered depending on tumor genetics.
2. Intraperitoneal Chemotherapy (Regional Chemotherapy)
   * Delivered directly into the abdominal cavity, often during surgery.
   * Two main methods:
     + Hyperthermic Intraperitoneal Chemotherapy (HIPEC): Heated chemotherapy solution (usually mitomycin C or oxaliplatin) is circulated in the abdomen for about 90-100 minutes after debulking surgery. Heat enhances drug penetration and effectiveness.
     + Early Postoperative Intraperitoneal Chemotherapy (EPIC): Chemotherapy administered through a catheter into the abdomen for several days after surgery.

## Common Chemotherapy Drugs and Side Effects

| **Drug** | **Common Side Effects** |
| --- | --- |
| Mitomycin C | Bone marrow suppression (low blood counts), nausea, vomiting, mouth sores, kidney toxicity |
| Oxaliplatin | Peripheral neuropathy (tingling/numbness in hands and feet), nausea, low blood counts, fatigue |
| Fluorouracil (5-FU) | Mouth sores, diarrhea, low blood counts, hand-foot syndrome (redness, swelling of palms/soles) |
| Irinotecan | Diarrhea (can be severe), nausea, vomiting, low blood counts |
| Leucovorin | Generally well tolerated; used to enhance 5-FU effectiveness |

## Side Effects Overview

* Bone marrow suppression: Leads to anemia, increased infection risk, and bleeding; monitored by regular blood tests.
* Gastrointestinal symptoms: Nausea, vomiting, diarrhea, and mouth sores are common but manageable with supportive medications.
* Peripheral neuropathy: Especially with oxaliplatin; may be temporary or persistent.
* Fatigue: Common during and after chemotherapy.
* Local side effects: Intraperitoneal chemotherapy may cause abdominal pain, inflammation, or infection risk.

## Surgical Treatment and Chemotherapy Integration

* Cytoreductive (debulking) surgery removes visible tumors and affected tissues.
* HIPEC is often performed immediately after surgery to kill microscopic cancer cells.
* Systemic chemotherapy may be given before or after surgery depending on disease extent.

## **Genetic Mutations and Their Implications**

* Subtypes and Mutation Frequencies:  
  Appendix cancer consists mainly of five subtypes:
  + *Mucinous adenocarcinomas* (~46%)
  + *Adenocarcinomas* (~30%)
  + *Goblet cell carcinoids* (~12%)
  + *Pseudomyxoma peritonei (PMP)* (~7.7%)
  + *Signet ring cell carcinomas* (~5.2%)
* Common Mutated Genes:
  + GNAS:
    - Frequently mutated in mucinous adenocarcinomas (52%) and PMP (72%).
    - This mutation is rare in colon cancer but common in appendix cancer.
    - Tumors with *GNAS* mutations are associated with a better prognosis, with median survival around 10 years.
    - *GNAS* mutations activate the cAMP pathway and link to the RAS–RAF–MEK–ERK signaling pathway, promoting cell proliferation and angiogenesis.
  + KRAS:
    - Mutated in many appendiceal cancers, especially mucinous neoplasms.
    - Mutations typically occur at codon 12, activating the RAS–RAF–MEK–ERK pathway, stimulating tumor growth.
  + TP53:
    - Tumor suppressor gene frequently mutated in adenocarcinomas (up to 47%) and signet ring cell carcinomas.
    - Associated with poorer prognosis, with median survival around 3 years.
    - Mutations lead to loss of programmed cell death and genomic instability.
  + SMAD4:
    - Tumor suppressor involved in TGF-beta signaling; mutations contribute to tumor progression.
  + BRAF:
    - Mutated in a smaller subset; part of the MAPK pathway.
  + Other less frequent mutations include *BRCA1*, *CDKN1B*, *CDKN2A*, *MYC*, *PTEN*, and *TGFBR2*.
* Mutual Exclusivity and Co-mutations:
  + *GNAS* and *KRAS* mutations often co-occur, suggesting cooperative roles in tumorigenesis.
  + *GNAS* and *TP53* mutations are mutually exclusive, indicating different tumor pathways.
* Microsatellite Instability (MSI):
  + Rare in appendix cancers, mostly reported in adenocarcinomas.

**Doctor-patient conversation about appendix cancer**

Doctor:  
“Thank you for coming in today. I want to talk with you about your diagnosis. The tests show that you have appendix cancer, which is a rare type of cancer that starts in the appendix, a small pouch attached to the large intestine.”

Patient:  
“I didn’t even know you could get cancer there. What does this mean? How serious is it?”

Doctor:  
“Appendix cancer is quite different from colon cancer. It often grows slowly and can produce mucus inside the abdomen. Sometimes, the cancer causes the appendix to rupture, which can spread cancer cells and mucus throughout the abdominal cavity. This condition is called pseudomyxoma peritonei.”

Patient:  
“That sounds scary. Can it be treated?”

Doctor:  
“Yes, there has been significant progress in treating appendix cancer. The main treatment is a specialized surgery called cytoreductive surgery, where we remove as much tumor and mucus as possible. After that, we use a heated chemotherapy treatment directly inside the abdomen, called HIPEC (Hyperthermic Intraperitoneal Chemotherapy), which helps kill any remaining cancer cells.”

Patient:  
“What are the chances of survival?”

Doctor:  
“Thanks to these treatments, about 75% of patients can be cured or live many years after treatment. Some patients live 20, 25, or even 30 years after their surgery and HIPEC. This is a big improvement compared to the past.”

Patient:  
“What should I expect from the surgery and treatment?”

Doctor:  
“The surgery can be extensive because we try to remove all visible tumors. HIPEC is done during the operation and involves circulating heated chemotherapy in your abdomen for about 90 minutes. Recovery takes time, and you may experience side effects like fatigue, nausea, or abdominal discomfort, but we will support you through this.”

Patient:  
“Will I need other treatments after surgery?”

Doctor:  
“That depends on your specific case. Sometimes, additional systemic chemotherapy is recommended. We will tailor your treatment plan based on tumor type, spread, and your overall health.”

Patient:  
“Is this a common cancer? How did it happen to me?”

Doctor:  
“Appendix cancer is rare and can be difficult to diagnose early because symptoms are often vague, like abdominal bloating or discomfort. Sometimes it’s found incidentally during surgery for suspected appendicitis or ovarian cysts. The exact cause isn’t always clear.”

Patient:  
“Is there anything I can do to prepare or help with recovery?”

Doctor:  
“Maintaining good nutrition, staying as active as you can before surgery, and having a strong support system will help. We’ll also provide you with information and connect you with support groups and resources.”

Patient:  
“Thank you for explaining everything. It helps to know there is a plan.”

Doctor:  
“You’re welcome. We’re here to guide and support you through every step. Please feel free to ask questions anytime.”

### **What questions should I ask my healthcare provider?**

Learning all you can about your condition can help you make informed decisions about your health. Questions to ask your provider include:

## **What kind of appendix tumor do I have?**

Appendix tumors can be of several types, mainly classified by the cells they originate from:

* Carcinoid (neuroendocrine) tumors: Most common, usually slow-growing, often found at the appendix tip.
* Mucinous adenocarcinomas: Produce mucin (a jelly-like substance), can spread within the abdomen causing pseudomyxoma peritonei.
* Colonic-type adenocarcinomas: Similar to colon cancer, usually at the appendix base.
* Goblet cell carcinomas: Have features of both adenocarcinoma and neuroendocrine tumors, more aggressive than carcinoids.
* Signet-ring cell adenocarcinomas: Rare and aggressive subtype.
* Paragangliomas: Very rare, usually benign.

Your pathology report will specify the exact tumor type.

## **What size is the tumor?**

The tumor size is determined by imaging studies (CT, MRI) or during surgery and pathology examination. Tumor size helps guide staging and treatment decisions. Please ask your doctor for your tumor’s exact measurements.

## **What stage and grade of appendix cancer do I have?**

* Stage describes how far the cancer has spread (localized, regional, distant). Appendix cancer staging considers tumor size, lymph node involvement, and metastasis, often using the TNM system.
* Grade reflects how abnormal the cancer cells look under the microscope and how quickly they are likely to grow (low grade = slower, high grade = more aggressive).  
  Your oncologist will explain your specific stage and grade after reviewing your pathology and imaging.

## **What are my treatment options?**

* Surgery: Cytoreductive surgery to remove visible tumors is the mainstay.
* HIPEC (heated intraperitoneal chemotherapy): Often given during surgery to kill residual cancer cells in the abdomen.
* Systemic chemotherapy: May be recommended depending on tumor type, stage, and spread.
* Treatment plans are individualized based on tumor type, stage, and your overall health.

## When do I need to start treatment?

Treatment usually begins soon after diagnosis, especially if surgery is planned. Your care team will schedule surgery and any additional therapies promptly to optimize outcomes.

## Will I be able to work while getting cancer treatment?

This depends on your treatment type, side effects, and overall health. Surgery and chemotherapy can cause fatigue and require recovery time, so many patients take time off work during intensive treatment. Your healthcare team can help you plan and manage work alongside treatment.

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### **Cardiac tumors**

Cardiac tumors (also called heart tumors) are growths that form in your heart. They can be either benign (noncancerous) or malignant (cancerous). Some are harmless or easily treatable, but others can be fatal. In general, an earlier diagnosis can lead to prompt treatment and better outcomes for people with cardiac tumors.

Cardiac tumors range in size and shape. Some are pedunculated, meaning they grow on a stalk. Heart tumors may be smaller than 1 centimeter in diameter or as big as 15 centimeters. Their size and location within your heart impact your symptoms and need for treatment.

### **Types of cardiac tumors**

There are many types of cardiac tumors. Doctors classify them based on how they develop. Heart tumors that begin in your heart — rather than spreading from another part of your body to your heart — are called primary heart tumors. Primary heart tumors are usually noncancerous but are sometimes cancerous.

When cancer elsewhere in your body spreads to your heart, those tumors are called metastatic heart tumors. Metastatic heart tumors are always cancerous because they result from cancer that’s already in your body.

#### **Noncancerous primary heart tumors**

About 75% to 95% of all primary heart tumors are noncancerous. But they can still be dangerous if they interfere with your heart function, and can pose a risk of stroke if left untreated.

Noncancerous primary heart tumors that develop in adults include:

* Myxoma. This is the most common noncancerous primary heart tumor (about 50% of all cases). It needs to be removed through surgery to prevent serious complications like an embolism. Myxomas usually develop in your left atrium.
* Papillary fibroelastoma. This is the second most common noncancerous primary heart tumor. It can affect people at any age, but it’s usually diagnosed in people over age 60. About 80% of the time, this tumor grows on heart valves (usually your aortic or mitral valve). Even if you don’t have symptoms, your provider will recommend surgery to reduce your risk of an embolism.
* Lipoma. This tumor affects people of many different ages. The tumor itself varies in its presentation. It may be small, or it may be very large. Lipomas usually develop in your left ventricle, right atrium or atrial septum (the wall that separates the top chambers of your heart).
* Hemangioma. These tumors have been diagnosed across the lifespan, from infants to people 65 years old. They usually don’t cause symptoms. So, they’re often diagnosed through tests for other issues. Hemangiomas often occur along with tumors in your gastrointestinal tract or skin.

Noncancerous primary heart tumors that develop in infants and children include:

* Cardiac rhabdomyoma. This is the most common type of heart tumor in infants and children. Rhabdomyomas grow in clusters and usually go away on their own without treatment.
* Teratoma. This tumor typically develops on the pericardium (the sac that surrounds your child’s heart). It can also grow from the base of the major blood vessels connected to their heart.
* Fibroma. Unlike a rhabdomyoma, a fibroma appears as a single tumor. It usually grows within the muscle of your child’s ventricles. Your child will likely need surgery to remove this tumor since it can cause serious heart problems.
* Hamartoma. This tumor is also called histiocytoid cardiomyopathy or Purkinje cell hamartoma. It may affect your child’s heart rhythm.

#### **Cancerous primary heart tumors**

About 5% to 25% of all primary heart tumors are cancerous. Among those, the most common form is sarcoma.

Sarcoma affects 50% to 75% of people with heart cancer. Sarcoma has many subtypes. Two of the most common include:

* Angiosarcoma. This is the most common subtype in adults. An angiosarcoma often develops in your right atrium or pericardium.
* Rhabdomyosarcoma. This is the most common subtype in infants and children. But it can also affect adults. Rhabdomyosarcomas often form in groups and can develop in any heart chamber.

Less common forms of cancerous primary heart tumors include:

* Malignant fibrous histiocytoma. This tumor often develops in your left atrium and may block your mitral valve, causing impaired blood flow in the chambers of your heart.
* Lymphoma. Usually, lymphoma (a cancer of white blood cells) develops in your lymph nodes, spleen or bone marrow. Rarely, it develops in your heart. This usually happens in people who have AIDS.

#### **Primary heart tumors that can be either noncancerous or cancerous**

Some tumors that begin in your heart can be either noncancerous or cancerous. These include:

* Mesothelioma. If this tumor develops in your pericardium, it’s cancerous. Rarely, though, it can begin in your atrioventricular node (part of your heart’s electrical system). In that case, it’s noncancerous.
* Paraganglioma. This tumor usually develops at the base of your heart.

#### **Metastatic heart tumors**

Metastatic heart tumors are cancerous tumors that have spread to your heart from somewhere else in your body. Cancers that may spread to your heart include:

* Melanoma.
* Lung cancer.
* Breast cancer.
* Lymphoma.
* Kidney cancer.
* Esophageal cancer.

### **Where are cardiac tumors located?**

Cardiac tumors can be located in many different parts of your heart. Both primary and metastatic heart tumors may form in the:

* Endocardium, which is the tissue that lines your heart chambers.
* Myocardium, which is your heart muscle.
* Heart valves, which are the “doors” that manage blood flow through your heart.
* Pericardium, which is the sac that surrounds your heart.

### **Who is affected by cardiac tumors?**

Cardiac tumors can affect anyone at any age, depending on the form. Some forms (like teratomas) develop while a fetus is still in the uterus. Other forms develop during childhood or various stages of adulthood.

Myxomas are two to four times more common among females than males.

Sarcomas are more common in middle-aged adults. The average age at diagnosis is 44.

Primary heart tumors (noncancerous and cancerous) affect fewer than 1 in 2,000 people. Of those, noncancerous tumors are much more common than cancerous ones.

Metastatic heart tumors are more common than primary heart tumors. They affect:

* About 10% of people who have lung cancer.
* About 10% of people who have breast cancer.
* Between 50% and 65% of people who have melanoma.

### **How do heart tumors affect my body?**

Heart tumors affect your body in many different ways. Cancerous heart tumors can spread elsewhere in your body, such as your lungs. Non cancerous heart tumors don’t spread but can cause heart and vascular problems, including:

* Arrhythmias.
* Blood clots and thromboembolism (a blood clot that blocks your blood flow).
* Blood flow problems within your heart.
* Heart attack.
* Heart failure.
* Heart murmurs.
* Hypotension.
* Pericardial effusion.
* Pericarditis.
* Valve damage.

How a tumor affects your heart depends on the tumor’s form and exactly where it’s located. For example, tumors that grow from your heart valves can interfere with blood flow in your heart or lead to blood clots. Tumors in your heart muscle may cause heart failure or arrhythmias.

If you’ve been diagnosed with a heart tumor, your provider will tell you where it’s located and how it may affect your heart.

## **Symptoms and Causes**

The symptoms of cardiac heart tumors are all across the board. They vary based on the form of tumor you have and where it’s located in your heart. Some people have no symptoms or very mild symptoms. Others have symptoms that signal life-threatening heart problems.

Many cardiac tumor symptoms are what doctors call “non-specific.” That means lots of different health problems could trigger these symptoms, not just heart tumors. So, if you have these symptoms, it’s not always obvious you have a heart tumor. It’s important to tell your healthcare provider about your symptoms so they can look for the cause.

Generally, people with cancerous heart tumors have symptoms that begin suddenly and get worse quickly. Symptoms of noncancerous heart tumors may develop more gradually.

Signs and symptoms of cardiac tumors include:

* Chest discomfort.
* Dizziness and fainting.
* Fatigue.
* Fever and chills.
* Heart palpitations.
* Joint pain.
* Loss of appetite.
* Night sweats.
* Petechiae.
* Shortness of breath.
* Swelling in your legs.
* Weight loss without another cause.

### **What causes cardiac tumors?**

It’s not always clear what causes primary heart tumors. Genetic syndromes (like Carney complex) may play a role in causing some noncancerous primary heart tumors.

The spread of cancer from one part of your body (like your lungs or skin) to your heart causes metastatic heart tumors.

## **Diagnosis and Tests**

Cardiac tumors are diagnosed through imaging tests. Your provider may suspect you have a heart tumor and run some tests to find out. Or, they may run tests for other reasons and find a tumor without expecting it.

When someone has cancer elsewhere in their body along with sudden heart problems, their provider may suspect a heart tumor. So, imaging tests can check if the cancer has spread to their heart.

Primary heart tumors are often difficult to diagnose because signs and symptoms are similar to those of other conditions. Providers may suspect a tumor in people who have symptoms of heart failure without a clear cause. But usually, providers diagnose primary heart tumors through tests they’ve ordered to check for other conditions. These are known as incidental findings.

Most heart tumor signs and symptoms are nonspecific and could indicate many possible problems. But there’s one sign unique to heart tumors. Your provider may be able to hear a characteristic “tumor plop” when listening to your heart through a stethoscope. They’ll hear this sound if the tumor physically blocks your mitral valve. It’s similar to what your provider would hear if you had mitral valve stenosis.

So, if your provider hears this sound, they may suspect you have a heart tumor, especially if you don’t have risk factors for mitral valve stenosis.

### **What tests will be done to diagnose cardiac tumors?**

Imaging tests are essential for diagnosing, treating and monitoring heart tumors. Your provider may run one or more of the following tests to reach a diagnosis:

* Transthoracic echocardiogram. This form of echo is helpful for finding tumors in your ventricles (lower chambers of your heart).
* Transesophageal echocardiogram. This form of echo is helpful for finding tumors in your atria (upper chambers of your heart).
* Cardiac MRI. This test helps identify details about the tumor, like whether it’s cancerous.
* Contrast-enhanced cardiac CT scans. This test is useful for people who have implanted devices and can’t undergo an MRI. It’s also valuable for evaluating your entire chest area (including lungs and blood vessels) and your coronary arteries.
* PET scan. This test is sometimes used to check if cancer in another part of your body has spread to your heart.

## **Management and Treatment**

Treatment options for cardiac tumors vary based on the type of tumor.

* Noncancerous primary heart tumors: Surgery is very successful at removing these tumors if they’re small. Larger tumors may be impossible to remove. Your provider or your child’s provider will recommend surgery if the tumor interferes with heart function. Children who have surgery to remove a fibroma may also need reconstructive surgery to fix damage to their heart.
* Cancerous primary heart tumors: These tumors can’t be removed and are often fatal. Chemotherapy or radiation may be used to slow the cancer’s progression. Your provider may also provide medications to manage complications.
* Metastatic heart tumors: Treatment depends on the source of the cancer. It may include chemotherapy or surgical removal of the tumor. Your provider may insert tubes in your chest to drain excess fluid from the tumor. They may also inject medications into your heart to slow tumor growth or combat fluid buildup.

## **Outlook / Prognosis**

Your outlook depends on the type of tumor you have and how early it’s diagnosed. Overall, an earlier diagnosis leads to better outcomes. But some cancerous tumors spread aggressively and are difficult or impossible to cure. Research shows:

* Myxomas can usually be removed successfully through surgery.
* Cancerous primary heart tumors are often fatal. These tumors spread quickly or come back after treatment. Your outlook depends on the tumor size, how much it’s spread and how early the cancer has been diagnosed.
* Metastatic heart tumors are usually fatal. People with these tumors face poor long-term outcomes due to the cancer’s aggressive spread.

### **How long can you live with a cardiac tumor?**

Your provider will discuss your individual prognosis with you. In general, people with noncancerous heart tumors have a better prognosis than people with cancerous tumors.

Cancerous primary heart tumors reduce your life expectancy. Overall:

* About 50% of people live one year after diagnosis.
* About 24% live three years.
* About 19% live five years.

Life expectancy also depends on the form of heart cancer.

* Sarcoma: People with sarcoma survive an average of nine to 17 months following diagnosis.
* Lymphoma: People with lymphoma survive an average of seven months. With treatment, they may survive up to five years. Without treatment, they may only survive for one month.
* Cancerous paraganglioma: This condition is often treatable. About 84% of people survive 10 years after a successful surgery. But there’s a 50% chance of the cancer coming back. You’ll need routine imaging tests to check for recurrence.

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

If you’ve been diagnosed with a cardiac tumor, it’s important to closely follow your provider’s guidance. Your provider will tell you how often you need to come in for appointments and what your treatment plan will be. They may also recommend genetic testing for you and for your family members.

If you’ve had surgery to remove a tumor, you’ll need regular follow-ups with your provider and routine imaging tests. These tests allow your provider to check if any tumors have returned. They also allow your provider to check your heart function and treat any issues that come up.

If your child was diagnosed with a cardiac tumor, their provider will explain next steps. Your child may need treatment right away.

**Differential Diagnosis (DDX) of Cardiac Tumors**

## 1. Primary Cardiac Tumors

## Benign Tumors (Most common)

* Myxoma
  + Most frequent primary cardiac tumor (about 75% of benign tumors).
  + Usually located in the left atrium (around fossa ovalis).
  + Features: pedunculated, smooth or lobulated surface, may cause obstruction or embolism.
* Rhabdomyoma
  + Most common in children, often associated with tuberous sclerosis.
* Fibroma
  + Usually in ventricles, can cause arrhythmias.
* Papillary fibroelastoma
  + Often found on valves, small and mobile.
* Lipoma
  + Fatty tumors, usually asymptomatic.
* Hemangioma
  + Vascular tumors, rare.
* Paraganglioma
  + Rare neuroendocrine tumor, may secrete catecholamines.

## Malignant Tumors (Primary)

* Angiosarcoma
  + Most common primary malignant cardiac tumor.
  + Typically involves the right atrium, aggressive with infiltration and hemorrhagic necrosis.
* Rhabdomyosarcoma
  + Occurs in children and adults, can arise in any chamber.
* Fibrosarcoma
  + Rare, aggressive.
* Primary cardiac lymphoma
  + Usually non-Hodgkin lymphoma involving the heart, often right atrium.

## 2. Secondary (Metastatic) Cardiac Tumors

* Much more common than primary cardiac tumors.
* Common primary sources: lung cancer, breast cancer, melanoma, lymphoma, leukemia, renal cell carcinoma.
* Usually involve pericardium but can invade myocardium or endocardium.
* Often present with pericardial effusion or tamponade.

## 3. Non-neoplastic Masses

* Thrombus
  + Usually located in areas of low flow (e.g., left atrial appendage in atrial fibrillation).
  + Differentiated by imaging techniques such as contrast echocardiography and cardiac MRI (thrombi are avascular and appear black on late gadolinium enhancement).
* Vegetations (infective endocarditis)
  + Usually attached to valves, associated with infection.

**EPIDEMIOLOGY**

Primary cardiac tumors are much rarer than secondary malignant lesions, occurring in about 0.001% to 0.3% of autopsies. Almost 75% to 90% of primary cardiac tumors excised surgically are benign. Cardiac myxomas have wide recognition as the most common primary benign cardiac neoplasm of adulthood, representing nearly 80% of benign tumors. Secondary malignant disease of the heart and pericardium is considerably more common than primary cardiac malignant disease; in some estimates, secondary malignant cardiac cancers are 30 to 1000 times more common.

In a random autopsy series, the frequency of metastatic involvement was 0.4%; in patients with confirmed cancer, cardiac involvement can be as high as 20%. Spread to the heart is generally via direct tumor extension, venous/lymphatic spread, or arterial metastasis. The most common underlying malignant diseases with secondary cardiac involvement are carcinoma of the lung, breast, esophagus, stomach, kidneys, melanoma, lymphoma, and leukemia

**Treatment of Cardiac Tumors: Drug Information and Side Effects**

* Benign tumors (e.g., myxomas, papillary fibroelastomas) are primarily treated with surgical excision, often curative with low recurrence.
* Malignant primary cardiac tumors (e.g., sarcomas, lymphomas) have a poor prognosis and usually require multimodal therapy including surgery, chemotherapy, and radiation.
* Metastatic cardiac tumors are treated based on the primary cancer origin, often with systemic chemotherapy and palliative care.

## **Common Chemotherapy Drugs Used in Malignant Cardiac Tumors**

| **Drug** | **Description** | **Common Side Effects** |
| --- | --- | --- |
| Paclitaxel | Chemotherapy agent used in sarcomas and other cancers | Hair loss, neuropathy (tingling/numbness), nausea, low blood counts, fatigue |
| Doxorubicin | Anthracycline chemotherapy, effective in sarcomas and lymphomas | Cardiotoxicity (heart damage), nausea, hair loss, low blood counts |
| Cyclophosphamide | Alkylating agent used in lymphomas and sarcomas | Nausea, vomiting, low blood counts, hemorrhagic cystitis |
| Vincristine | Microtubule inhibitor used in lymphoma regimens | Peripheral neuropathy, constipation, low blood counts |
| Prednisone | Corticosteroid often combined with chemo for lymphoma | Increased appetite, mood changes, immune suppression |
| Rituximab | Monoclonal antibody targeting CD20 on B-cells, used in cardiac lymphoma | Infusion reactions, low blood counts, infections |

## Targeted and Supportive Therapies

* Everolimus and Sirolimus:  
  Used mainly for benign tumors like rhabdomyomas, especially in children; mTOR inhibitors that can shrink tumors. Side effects include mouth sores, infections, and fatigue.
* Radiation Therapy:  
  External beam radiation may be used for unresectable malignant tumors or as adjuvant therapy. Side effects depend on dose and location but can include fatigue, skin irritation, and potential cardiac damage.

## Side Effects and Management

* Cardiotoxicity:  
  Particularly with anthracyclines (doxorubicin), requiring cardiac monitoring before and during treatment.
* Bone Marrow Suppression:  
  Leads to anemia, increased infection risk, and bleeding; requires regular blood count monitoring.
* Neuropathy:  
  Common with paclitaxel and vincristine; may cause numbness or tingling in hands and feet.
* Gastrointestinal Effects:  
  Nausea, vomiting, diarrhea, and mouth sores are common but manageable with supportive care.
* Infusion Reactions:  
  With monoclonal antibodies like rituximab, premedication and monitoring during infusion are standard.

## Surgical and Other Treatments

* Surgical excision is the mainstay for benign tumors and selected malignant tumors where complete resection is possible.
* Heart transplantation or autotransplantation may be considered in select unresectable cases at specialized centers.
* Palliative care focuses on symptom management in advanced or unresectable cases.

**doctor-patient conversation about cardiac tumors**,

Doctor:  
“Thank you for coming in today. I want to discuss the results of your tests. You have a tumor in your heart, which is a rare condition. These tumors can be either benign (noncancerous) or malignant (cancerous), and the treatment and outlook depend on the type and size of the tumor.”

Patient:  
“That sounds serious. What kind of tumor do I have, and what does it mean?”

Doctor:  
“Based on your imaging and biopsy, your tumor is [insert tumor type, e.g., a myxoma, which is the most common benign heart tumor]. Benign tumors like myxomas usually grow slowly and can often be cured with surgery. Malignant tumors, such as sarcomas or lymphomas, are more aggressive and may require additional treatments like chemotherapy or radiation.”

Patient:  
“What symptoms should I expect, and how will this affect my heart?”

Doctor:  
“Cardiac tumors can cause symptoms by blocking blood flow, causing irregular heartbeats, or leading to embolism (small clots traveling to other parts of the body). Some patients have no symptoms, and the tumor is found incidentally. We will monitor your heart function closely and plan treatment to minimize these risks.”

Patient:  
“What are my treatment options?”

Doctor:  
“For benign tumors, surgery to remove the tumor is usually the best option and often curative. For malignant tumors, treatment involves a combination of surgery, chemotherapy, and sometimes radiation. In some cases where surgery is not possible, chemotherapy or radiation alone may be used to control symptoms.”

Patient:  
“Is the surgery risky? What about side effects from treatment?”

Doctor:  
“Any heart surgery carries risks, but these are carefully managed by our surgical team. Chemotherapy and radiation can have side effects like fatigue, nausea, and low blood counts, but we will support you through these. Some chemotherapy drugs can affect heart function, so we monitor you closely.”

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

Doctor:  
“After treatment, you will need regular follow-ups with imaging tests like echocardiograms or MRIs to check for tumor recurrence and to monitor your heart function. Initially, these may be every few months, then less frequently over time.”

Patient:  
“Are there support resources available?”

Doctor:  
“Yes, we have support groups, counseling services, and patient education materials. Our care team, including nurses and social workers, will help connect you with these resources.”

Patient:  
“What should I do next?”

Doctor:  
“We will schedule your surgery or treatment soon. Meanwhile, please keep track of any new symptoms and let us know immediately if you experience chest pain, shortness of breath, or fainting.”

Patient:  
“Thank you for explaining everything. It helps to know what to expect.”

Doctor:  
“You’re welcome. We are here to support you throughout your treatment. Please feel free to ask questions anytime.”

### **What questions should I ask my provider?**

Talk with your provider about your diagnosis, treatment plan and prognosis. You may want to ask:

## What type of tumor do I have? Is it cancerous?

Cardiac tumors can be benign (noncancerous) or malignant (cancerous). The most common benign tumor is a myxoma, often found in the left atrium. Other benign tumors include fibromas, papillary fibroelastomas, and rhabdomyomas (more common in children).  
Malignant tumors include angiosarcomas, rhabdomyosarcomas, and primary cardiac lymphomas. Your doctor will determine the exact type based on imaging and biopsy results. Benign tumors grow slowly and are often curable with surgery, while malignant tumors grow more rapidly and may spread.

## How might this tumor affect my heart?

The tumor’s effects depend on its size, location, and type:

* It may obstruct blood flow through heart chambers or valves, causing symptoms like shortness of breath or heart failure.
* It can cause arrhythmias by affecting the heart’s electrical system.
* Pieces of the tumor or associated clots can break off and cause embolisms (blockage of blood vessels elsewhere, like the brain or lungs).
* Malignant tumors may invade heart tissue or cause pericardial effusion (fluid around the heart), leading to tamponade (heart compression).
* Some tumors release substances causing systemic symptoms like fever, weight loss, or fatigue.

## What’s the best way to treat this tumor?

* For benign tumors, the preferred treatment is surgical removal, which is often curative.
* For malignant tumors, treatment usually involves a combination of surgery, chemotherapy, and radiation therapy, depending on tumor type and spread.
* In some cases, if surgery is not possible, chemotherapy or radiation alone may be used to control symptoms.
* Treatment plans are individualized by a multidisciplinary team.

## How soon do I need treatment?

Treatment is typically started as soon as possible after diagnosis, especially if the tumor is causing symptoms or risks complications like obstruction or embolism. Early surgery is often recommended for benign tumors to prevent complications.

## What’s my outlook following treatment?

* Patients with benign tumors like myxomas generally have an excellent prognosis after surgery, with low recurrence rates.
* The outlook for malignant tumors is more guarded; survival depends on tumor type, stage, and response to treatment. For example, the 5-year survival for malignant cardiac sarcomas is around 30%, while benign tumors have survival rates over 80%.
* Regular follow-up is important to monitor for recurrence or complications.

## How often do I need to come back for follow-ups or additional tests?

Follow-up schedules vary but typically include:

* Frequent visits (every few months) in the first 1-2 years after treatment with imaging tests (echocardiogram, MRI) to check for tumor recurrence and heart function.
* If stable, visits may be spaced out to 6-12 months or yearly.
* Your doctor will tailor follow-up based on your tumor type and treatment.

## If your child has a heart tumor, ask their provider:

What type of tumor does my child have? Is it cancerous?  
Children often have different types of heart tumors, like rhabdomyomas, which are usually benign and may shrink over time, or rarer malignant tumors. Your child’s doctor will explain the diagnosis.

How might this tumor affect my child’s heart and overall health?  
Tumors can cause obstruction, arrhythmias, or heart failure. Some tumors may affect growth or cause systemic symptoms.

Will my child need surgery? If so, how soon?  
Surgery is often needed if the tumor causes symptoms or risks complications. The timing depends on the tumor’s size, location, and symptoms.

What’s the outlook for my child?  
Many benign tumors in children improve over time, especially rhabdomyomas. Malignant tumors have a more serious prognosis but treatment advances have improved outcomes.

What can I do at home to take care of my child?  
Ensure regular medical follow-ups, monitor for symptoms like difficulty breathing, fainting, or fatigue, and follow your healthcare team’s advice on activity and medications.

Which symptoms should I look out for? What should I do if I notice these symptoms?  
Watch for signs such as:

* Shortness of breath or difficulty breathing
* Fainting or dizziness
* Palpitations or irregular heartbeat
* Swelling in legs or abdomen
* Sudden weakness or neurological symptoms (possible embolism)  
  If you notice any of these, seek medical attention promptly.

REFERENCES

<https://my.clevelandclinic.org/health/diseases/22914-cardiac-tumor>

<https://www.ncbi.nlm.nih.gov/books/NBK537144/#article-18896.s9>

<https://www.medindia.net/drugs/medical-condition/heart-cancer.htm>

Vaginal cancer is a growth of cells that starts in the vagina. The cells multiply quickly and can invade and destroy healthy body tissue.

The vagina is part of the female reproductive system. It's a muscular tube that connects the uterus with the outer genitals. The vagina is sometimes called the birth canal.

Cancer that begins in the vagina is rare. Most cancer that happens in the vagina starts somewhere else and spreads to the vagina.

Vaginal cancer that's diagnosed when it's confined to the vagina has the best chance for a cure. When the cancer spreads beyond the vagina, it's much harder to treat.

CAUSES

Vaginal cancer begins when cells in the vagina develop changes in their DNA. A cell's DNA holds the instructions 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 would 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.

Most DNA changes that lead to vaginal cancers are thought to be caused by human papillomavirus, also called 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 vaginal cancer**

Vaginal cancer is divided into different types based on the type of cells affected. Vaginal cancer types include:

* **Vaginal squamous cell carcinoma**, which begins in thin, flat cells called squamous cells. The squamous cells line the surface of the vagina. This is the most common type.
* **Vaginal adenocarcinoma**, which begins in the glandular cells on the surface of the vagina. This is a rare type of vaginal cancer. It's linked to a medicine called diethylstilbestrol that was once used to prevent miscarriage.
* **Vaginal melanoma**, which begins in the pigment-producing cells, called melanocytes. This type is very rare.
* **Vaginal sarcoma**, which begins in the connective tissue cells or muscles cells in the walls of the vagina. This type is very rare.

## **Risk factors**

Factors that may increase your risk of vaginal cancer include:

### **Increasing age**

The risk of vaginal cancer increases with age. Vaginal cancer happens most often in older adults.

### **Exposure to human papillomavirus**

Human papillomavirus, also called HPV, is a common virus that's passed through sexual contact. HPV is thought to cause many types of cancer, including vaginal cancer. For most people, HPV infection goes away on its own and never causes any problems. But for some, HPV can cause changes in the cells of the vagina that increase the risk of cancer.

### **Smoking**

Smoking tobacco increases the risk of vaginal cancer.

### **Exposure to miscarriage prevention medicine**

If your parent took a medicine called diethylstilbestrol while pregnant, your risk of vaginal cancer might be increased. Diethylstilbestrol, also called DES, was once used to prevent miscarriage. It's linked to a type of vaginal cancer called clear cell adenocarcinoma.

## **Complications**

Vaginal cancer can spread to other parts of the body. It most often spreads to the lungs, liver and bones. When cancer spreads, it's called metastatic cancer.

## **Prevention**

There is no sure way to prevent vaginal cancer. However, you may lower your risk if you:

### **Seek out regular pelvic exams and Pap tests**

Regular pelvic exams and Pap tests are used to look for signs of cervical cancer. Sometimes vaginal cancer is found during these tests. Ask your healthcare team how often you should undergo cervical cancer screening tests and which tests are best for you.

### **Consider the HPV vaccine**

Receiving a shot to prevent HPV infection may lower the risk of vaginal cancer and other HPV-related cancers. Ask your healthcare team whether an HPV vaccine is right for you.

SYMPTOMS

Vaginal cancer may not cause any symptoms at first. As it grows, vaginal cancer may cause signs and symptoms, such as:

* Vaginal bleeding that isn't typical, such as after menopause or after sex.
* Vaginal discharge.
* A lump or mass in the vagina.
* Painful urination.
* Frequent urination.
* Constipation.
* Pelvic pain.

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

Make an appointment with a doctor or other healthcare professional if you have any persistent symptoms that worry you.

DIAGNOSIS

ests and procedures used to diagnose vaginal cancer include:

* **Pelvic exam.** A pelvic exam allows a healthcare professional to inspect the reproductive organs. It's often done during a regular checkup. But it might be needed if you have symptoms of vaginal cancer.  
  During the exam, the healthcare professional carefully inspects the outer genitals. The health professional inserts two fingers of one hand into the vagina. At the same time, that person's other hand presses on the belly 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 changes in the vagina and cervix. Changes could be signs of cancer or other problems.
* **Inspecting the vagina with a magnifying instrument.** Colposcopy is an exam to look at the vagina with a special lighted magnifying instrument. Colposcopy helps to magnify the surface of the vagina to look for any changes that might be cancerous.
* **Removing a sample of vaginal tissue for testing.** A biopsy is a procedure to remove a sample of tissue to test for cancer cells. Often, a biopsy is done during a pelvic exam or a colposcopy exam. The tissue sample is sent to a lab for testing.

### **Staging**

If you're found to have vaginal cancer, your healthcare team may recommend tests to find the extent of the cancer. The size of the cancer and whether it has spread is called the cancer's stage. The stage indicates how likely the cancer is to be cured. It helps the healthcare team to create a treatment plan.

Tests used to find the vaginal cancer stage include:

* **Imaging tests.** Imaging tests may include X-rays, CT, MRI or positron emission tomography, also called PET.
* **Tiny cameras to see inside the body.** Procedures that use tiny cameras to see inside the body may help determine whether cancer has spread to certain areas. A procedure to look inside the bladder is called cystoscopy. A procedure to look inside the rectum is called proctoscopy.

Information from these tests and procedures is used to assign the cancer a stage. The stages of vaginal cancer range from 1 to 4. The lowest number means that the cancer is only in the vagina. As the cancer becomes more advanced, the stages get higher. A stage 4 vaginal cancer may have grown to involve nearby organs or spread to other parts of the body.

## **Treatment**

Treatment for most vaginal cancers often starts with radiation therapy and chemotherapy at the same time. For very small cancers, surgery might be the first treatment.

Your treatment options for vaginal cancer depend on several factors. This includes the type of vaginal cancer you have and its stage. You and your healthcare team work together to decide what treatments are best for you. Your team considers your goals for treatment and the side effects you're willing to accept.

Vaginal cancer treatment is usually coordinated by a doctor who specializes in treating cancers that affect the female reproductive system. This doctor is called a gynecologic oncologist.

### **Radiation therapy**

Radiation therapy uses powerful energy beams to kill cancer cells. The energy comes from X-rays, protons or other sources. Radiation therapy procedures include:

* **External radiation.** External radiation also is called external beam radiation. It uses a large machine to direct beams of radiation at precise points on your body.
* **Internal radiation.** Internal radiation also is called brachytherapy. It involves putting radioactive devices in the vagina or near it. Types of devices include seeds, wires, cylinders or other materials. After a set amount of time, the devices may be removed. Internal radiation is often used after external radiation.

Most vaginal cancers are treated with a combination of radiation therapy and low-dose chemotherapy medicines. Chemotherapy is a treatment that uses strong medicines to kill cancer cells. Using a low dose of chemotherapy medicine during radiation treatments makes the radiation more effective.

Radiation also can be used after surgery to kill any cancer cells that might be left behind.

### **Surgery**

Types of surgery that may be used to treat vaginal cancer include:

* **Removal of the vagina.** Vaginectomy is an operation to remove some or all of the vagina. It might be an option for small vaginal cancers that haven't grown beyond the vagina. It's typically used when the cancer is small and isn't near any important structures. If the cancer is growing near an important part, such as the tube that carries urine out of the body, surgery might not be an option.
* **Removal of many of the pelvic organs.** Pelvic exenteration is an operation to remove many of the pelvic organs. It might be used if cancer comes back or doesn't respond to other treatments. During pelvic exenteration, a surgeon may remove the bladder, ovaries, uterus, vagina and rectum. Openings are created in the abdomen to allow urine and waste to leave the body.

If your vagina is completely removed, you may choose to have surgery to make a new vagina. Surgeons use sections of skin or muscle from other areas of your body to form a new vagina.

A reconstructed vagina allows you to have vaginal intercourse. Sex may feel different after surgery. A reconstructed vagina lacks natural lubrication. It may lack feeling due to changes in the nerves.

### **Other options**

If other treatments don't control your cancer, these treatments might be used:

* **Chemotherapy.** Chemotherapy uses strong medicines to kill cancer cells. Chemotherapy might be recommended if your cancer has spread to other parts of your body or if it comes back after other treatments.
* **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. This might be an option if your cancer is advanced and other treatments haven't helped. Immunotherapy is often used to treat vaginal melanoma.
* **Clinical trials.** Clinical trials are experiments to test new treatment methods. While a clinical trial gives you a chance to try the latest treatment advances, a cure isn't guaranteed. If you're interested in trying a clinical trial, discuss it with your healthcare team.

### **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. 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.

## **Outlook / Prognosis**

### **What is the outlook for vaginal cancer?**

Your prognosis for vaginal cancer depends on the stage at which it’s diagnosed. Early-stage vaginal cancers can often be successfully treated, and you can go on to live a full life. Later-stage cancers are harder to treat and may require ongoing chemotherapy and other treatment options. For this reason, it’s important to get regular gynecological exams, even when you feel healthy. Seek medical advice at the first sign of symptoms.

## **Prevention**

### **How can I reduce my risk of getting vaginal cancer?**

You can’t prevent vaginal cancer, but you can reduce your risk.

* Get regular pelvic exams and Pap tests. Talk with your provider about how regularly you should be receiving routine checks from your gynecologist.
* Get the HPV vaccine. Talk to your provider about getting vaccinated against HPV. Currently, there are three FDA-approved vaccines available, Gardasil, Gardasil 9 and Cervarix.
* Don’t smoke. Smoking increases your risk of all cancers, including vaginal cancer.

## **Additional Common Questions**

### **Can you get cancer in your vagina?**

Yes. But it’s rare for cancer to begin in your vagina, as with vaginal cancer. More often, cancers that begin in other parts of your body spread to your vagina. Cancers that spread to your vagina most commonly begin in your cervix (cervical cancer) or the lining of your uterus (uterine cancer/endometrial cancer).

### **What cancer causes vaginal bleeding?**

Vaginal bleeding is a common symptom of multiple cancers, including vaginal cancer, cervical cancer, uterine cancer and [ovarian cancer.](https://my.clevelandclinic.org/health/diseases/4447-ovarian-cancer) But abnormal bleeding is a common sign of multiple conditions, not just cancer. Don’t assume you have cancer if you have unusual bleeding. Still, see your healthcare provider to get checked.

### **What does vaginal cancer feel like?**

The most common symptom of vaginal cancer is painless vaginal bleeding, which means you may not feel vaginal cancer at all. Less commonly, you may experience pain in your pelvis, painful urination or discomfort related to constipation.

[Vaginal Cancer: Causes, Symptoms, Types & Treatment](https://my.clevelandclinic.org/health/diseases/15579-vaginal-cancer#outlook-prognosis)

[Vaginal cancer - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/vaginal-cancer/diagnosis-treatment/drc-20352453)

### **What is vulvar cancer?**

Vulvar cancer is a rare [cancer](https://my.clevelandclinic.org/health/diseases/12194-cancer) that forms in the tissues of your [vulva](https://my.clevelandclinic.org/health/body/vulva). “Vulva” is the collective name for all the [female external sex organs](https://my.clevelandclinic.org/health/articles/sex-recorded-at-birth), or genitals. Your vulva includes:

* Opening of your [vagina](https://my.clevelandclinic.org/health/body/22469-vagina): The muscular canal for sex, childbirth and [menstruation (periods)](https://my.clevelandclinic.org/health/articles/10132-menstrual-cycle).
* Labia minora (inner lips): Tissue folds that surround your vaginal opening and extend above your clitoris.
* Labia majora (outer lips): Fleshy area that surrounds your inner lips.
* The outer part of your [clitoris](https://my.clevelandclinic.org/health/body/22823-clitoris): The sexually sensitive nub of flesh above your vaginal opening.
* Mons pubis: The rounded area in front of your pubic bones that becomes covered with hair at puberty.
* Opening of the urethra: The tube that allows urine (pee) to exit your body.
* [Perineum](https://my.clevelandclinic.org/health/body/24381-perineum): The patch of skin between your vagina and anus (butthole).

Vulvar cancer usually develops slowly over several years. Precancerous areas of tissue (lesions) typically develop first. Healthcare providers usually discover the abnormal growth in the outermost layer of your [skin](https://my.clevelandclinic.org/health/articles/10978-skin). These precancerous [lesions](https://my.clevelandclinic.org/health/diseases/24296-skin-lesions) are called vulvar intraepithelial neoplasia (VIN).

#### **Types of vulvar cancer**

Healthcare providers classify vulvar cancer based on the type of cells where the cancer starts. The most common types of vulvar cancer include:

* Vulvar squamous cell carcinoma: Approximately 90% of vulvar cancers are [squamous cell carcinomas](https://my.clevelandclinic.org/health/diseases/17480-squamous-cell-carcinoma). They develop in the cells on the surface of your skin.
* Vulvar melanoma: Approximately 5% of vulvar cancers are [melanomas](https://my.clevelandclinic.org/health/diseases/14391-melanoma). Melanomas develop rapidly and have a high risk of spreading to other areas of your body.

The remaining vulvar cancers are rare. They include:

* [Basal cell carcinoma](https://my.clevelandclinic.org/health/diseases/4581-basal-cell-carcinoma).
* Bartholin gland [adenocarcinoma](https://my.clevelandclinic.org/health/diseases/21652-adenocarcinoma-cancers).
* Paget disease of the vulva.
* [Sarcoma](https://my.clevelandclinic.org/health/diseases/17934-sarcoma).
* [Verrucous carcinoma](https://my.clevelandclinic.org/health/diseases/22286-verrucous-carcinoma).

#### **How common is vulvar cancer?**

Vulvar cancer is rare. Healthcare providers diagnose just under 6,500 new cases of vulvar cancer in the U.S. each year.

Nearly 80% of people diagnosed are over age 50, and over half of all diagnoses are in people over age 70. The average age at diagnosis is 68.

## **Symptoms and Causes**

### **What are the symptoms of vulvar cancer?**

The first noticeable signs of vulvar cancer are usually skin changes on your outer lips (labia majora) or inner lips (labia minora). But cancer can form anywhere on your vulva.

Vulvar cancer symptoms include:

* Color changes, including skin that looks darker or lighter than usual, or patches of white skin.
* Thickened or rough skin patches.
* Growths, including lumps, wart-like bumps or ulcers that don’t heal.
* [Itching](https://my.clevelandclinic.org/health/diseases/11879-pruritus) or burning that doesn’t improve.
* Bleeding that’s unrelated to menstruation (periods).
* Tenderness and pain, potentially during sex or when you’re peeing.

See your healthcare provider if you have one or more of these symptoms. Vulvar cancer symptoms usually don’t appear in the early stages, so it’s important to get checked as soon as possible.

Still, many of these symptoms are also common in noncancerous conditions. Your provider can tell you whether these changes are signs of vulvar cancer or a different condition.

### **What causes vulvar cancer?**

With vulvar cancer, cells begin multiplying out of control. Without treatment, these cancer cells can spread to other parts of your body.

The most common type of vulvar cancer, vulvar squamous cell carcinoma, arises in association with one of two conditions:

* [Human papillomavirus](https://my.clevelandclinic.org/health/diseases/11901-hpv-human-papilloma-virus) (HPV) infection: A common sexually transmitted infection ([STI](https://my.clevelandclinic.org/health/diseases/9138-sexually-transmitted-diseases--infections-stds--stis)) that spreads through skin-to-skin contact. Some types of HPV increase your risk of certain cancers, including [cervical cancer](https://my.clevelandclinic.org/health/diseases/12216-cervical-cancer), [anal cancer](https://my.clevelandclinic.org/health/diseases/6151-anal-cancer), [rectal cancer](https://my.clevelandclinic.org/health/diseases/21733-rectal-cancer) and vulvar cancer.
* [Lichen sclerosus](https://my.clevelandclinic.org/health/diseases/16564-lichen-sclerosus): A chronic (lifelong) skin condition. Lichen sclerosus causes [inflammation](https://my.clevelandclinic.org/health/symptoms/21660-inflammation) and other symptoms, such as skin changes and itching, on your vulva.

#### **Risk factors**

Risk factors for vulvar cancer include:

* Age: Your likelihood of developing vulvar cancer increases with age.
* Exposure to HPV: Not all strains of HPV cause cancer, but some can lead to cell changes that eventually become vulvar cancer.
* Skin conditions involving your vulva: Growths associated with lichen sclerosus may progress to vulvar cancer.
* Vulvar intraepithelial neoplasia (VIN): VIN is a precancerous condition that can progress to vulvar cancer if it’s not treated.
* [Human immunodeficiency virus (HIV) infection](https://my.clevelandclinic.org/health/diseases/4251-hiv-aids): A weakened [immune system](https://my.clevelandclinic.org/health/articles/21196-immune-system) from a condition like HIV can make it harder for your body to fight cancer.
* [Smoking](https://my.clevelandclinic.org/health/articles/17488-smoking): Smoking raises your risk of developing multiple cancer types, including vulvar cancer.

## **Diagnosis and Tests**

### **How is vulvar cancer diagnosed?**

Your healthcare provider will ask about your medical history, potential risk factors and symptoms. Diagnosis often involves multiple tests.

#### **Tests to diagnose vulvar cancer**

Tests may include:

* [Pelvic exam](https://my.clevelandclinic.org/health/diagnostics/17343-pelvic-exam): Your provider will visually inspect your vulva, checking for unusual skin changes. They’ll insert one or two gloved, lubricated fingers inside your vagina to feel for any lumps or other signs of cancer. They may use a similar technique to check your rectum. They may use a tool called a [speculum](https://my.clevelandclinic.org/health/drugs/24238-speculum) to widen your vagina so they can check for abnormalities.
* [Pap smear](https://my.clevelandclinic.org/health/diagnostics/4267-pap-smear): Your provider may take a sample of cells during the pelvic exam and test them for cancerous changes. They may perform an [HPV test](https://my.clevelandclinic.org/health/diagnostics/22163-human-papillomavirus-hpv-test) on the sample to see if you have an infection.
* [Colposcopy](https://my.clevelandclinic.org/health/diagnostics/4044-colposcopy): Your provider may use a lighted, magnifying instrument called a colposcope to view your vulva, vagina and [cervix](https://my.clevelandclinic.org/health/body/23279-cervix) (the organ between your vagina and [uterus](https://my.clevelandclinic.org/health/body/22467-uterus)) in more detail. They may apply a special solution that can highlight abnormal cells, making them easier to see.
* [Biopsy](https://my.clevelandclinic.org/health/diagnostics/15458-biopsy-overview): Your provider may remove a sample of abnormal tissue to test it for cancer cells. A biopsy is the only way to know for sure whether you have vulvar cancer.

#### **Tests to determine cancer spread**

If you have cancer, your provider will perform additional tests to see if it’s spread beyond your vulva. Without treatment, vulvar cancer may spread to your vagina or other nearby organs, [lymph nodes](https://my.clevelandclinic.org/health/body/23131-lymph-nodes) in your pelvis and eventually your bloodstream. Cancer that’s spread ([metastatic cancer](https://my.clevelandclinic.org/health/diseases/22213-metastasis-metastatic-cancer)) is harder to treat.

Tests may include:

* Scope exams: You may receive a [cystoscopy](https://my.clevelandclinic.org/health/diagnostics/16553-cystoscopy) to check for cancer spread in your urethra (the tube that carries your pee) or bladder. A [proctoscopy](https://my.clevelandclinic.org/health/treatments/10749-proctoscopy-rigid-sigmoidoscopy) checks for cancer cells in your rectum or anus.
* Imaging tests: [X-rays](https://my.clevelandclinic.org/health/diagnostics/21818-x-ray), computed tomography ([CT](https://my.clevelandclinic.org/health/diagnostics/4808-ct-computed-tomography-scan)) scans, magnetic resonance imaging ([MRI](https://my.clevelandclinic.org/health/diagnostics/4876-magnetic-resonance-imaging-mri)) and positron emission tomography ([PET](https://my.clevelandclinic.org/health/diagnostics/10123-pet-scan)) scans can show if the cancer has spread from your vulva to other tissues.
* [Sentinel node biopsy](https://my.clevelandclinic.org/health/diagnostics/9192-sentinel-node-biopsy): Your provider may remove the lymph node closest to your tumor (the sentinel node) to test for cancer cells. With vulvar cancer, tumors usually drain into sentinel lymph nodes in your groin.

### **What are the stages of vulvar cancer?**

Vulvar [cancer staging](https://my.clevelandclinic.org/health/diagnostics/22607-cancer-stages-grades-system) allows healthcare providers to determine if your cancer’s spread beyond your vulva. This information guides treatment decisions. There are four main stages:

* Stage I: Early-stage vulvar cancer is only on your vulva or perineum (area between your rectum and vagina). Stage I consists of Stages IA or IB based on [tumor](https://my.clevelandclinic.org/health/diseases/21881-tumor) size and how far it reaches into nearby tissue.
* Stage II: The tumor (of any size) has spread into the lower part of your [urethra](https://my.clevelandclinic.org/health/body/23002-urethra), the lower part of your vagina or [anus](https://my.clevelandclinic.org/health/body/24784-anus-function).
* Stage III: Cancer has spread to one or more nearby lymph nodes. Stage III consists of Stages IIIA, IIIB, and IIIC based on the number and size of the lymph nodes involved.
* Stage IV: Cancer has spread into the upper part of your urethra, vagina or other body parts. Stage IV consists of Stages IVA and IVB based on if the spread is localized near your vulva or spread distantly.

Ask your healthcare provider to explain the details of what your cancer stage means for your treatment.

## **Management and Treatment**

### **How is vulvar cancer treated?**

Your treatment depends on factors like your general health, cancer stage and whether your healthcare provider recently diagnosed your cancer or if it’s [recurred](https://my.clevelandclinic.org/health/diseases/24872-cancer-recurrence) (come back). Your provider can explain how your treatment plan is best suited for your diagnosis.

#### **Surgery**

Surgery is the most common treatment for cancer of the vulva. The goal is to remove all the cancer while preserving your sexual function. Types of surgery include:

* Laser surgery: This surgery uses a laser beam to make bloodless cuts in tissue or to remove cancerous surface lesions.
* Local excision: This surgery removes the cancer and a small-to-large amount of normal tissue around the cancer. Sometimes, providers remove nearby lymph nodes to test for cancer cells or to remove lymph nodes when there’s evidence of cancer.
* Vulvectomy: This procedure removes part or all of your vulva and possibly some nearby lymph nodes. Your provider may use [skin grafts](https://my.clevelandclinic.org/health/treatments/21647-skin-graft) to replace removed skin.
* [Pelvic exenteration](https://my.clevelandclinic.org/health/treatments/22455-pelvic-exenteration): This surgery removes your lower [colon](https://my.clevelandclinic.org/health/body/22134-colon-large-intestine), [rectum](https://my.clevelandclinic.org/health/body/24785-rectum-function), [bladder](https://my.clevelandclinic.org/health/body/25010-bladder), cervix, vagina, [ovaries](https://my.clevelandclinic.org/health/body/22999-ovaries) and nearby lymph nodes. Your healthcare provider will create openings to allow urine and stool to flow from your body into a collection bag.

#### **Radiation therapy**

[Radiation therapy](https://my.clevelandclinic.org/health/treatments/17637-radiation-therapy) uses X-rays or other high-energy sources to kill cancer cells. The most common delivery method for vulvar cancer treatment is external beam radiation therapy ([EBRT](https://my.clevelandclinic.org/health/treatments/24008-external-beam-radiation-therapy-ebrt)). EBRT uses a machine to deliver radiation through your skin to the targeted cancer site.

Often, people receive radiation therapy and chemotherapy together (chemoradiation). You may receive radiation before surgery to shrink a tumor or after surgery to destroy any remaining cancer cells.

#### **Chemotherapy**

[Chemotherapy](https://my.clevelandclinic.org/health/treatments/16859-chemotherapy) uses [drugs](https://my.clevelandclinic.org/health/treatments/24323-chemotherapy-drugs) to attack cancer cells throughout your body. Your healthcare provider may inject the medicine into a [vein](https://my.clevelandclinic.org/health/body/23360-veins) or [muscle](https://my.clevelandclinic.org/health/body/21887-muscle), or you may take a pill. You may receive a lotion that you can apply directly to your vulva. This form of chemotherapy attacks cancer more locally — in the specific area.

[Cisplatin](https://my.clevelandclinic.org/health/drugs/18018-cisplatin-injection) (Platinol®, Platinol -AQ®) and [fluorouracil](https://my.clevelandclinic.org/health/drugs/19329-fluorouracil-5-fu-skin-cream-or-solution) (Carac®) are commonly prescribed chemotherapy drugs for vulvar cancer.

#### **Immunotherapy**

[Immunotherapy](https://my.clevelandclinic.org/health/treatments/11582-immunotherapy) helps your body’s immune system identify cancer cells and fight them more effectively. [Imiquimod cream](https://my.clevelandclinic.org/health/drugs/20093-imiquimod-skin-cream) (Aldara®, Zyclara®) is a common immunotherapy medication used to treat vulvar cancer.

### **What follow-up should I expect after vulvar cancer treatment?**

Your healthcare provider may perform tests at various checkpoints after treatment to monitor your condition and ensure the cancer hasn’t returned.

Testing often involves the same procedures used to diagnose and stage vulvar cancer.

## **Outlook / Prognosis**

### **Is vulvar cancer serious?**

It can be. Untreated vulvar cancer is life-threatening. Cancer that’s spread to your lymph nodes or other body parts is much harder to treat than cancer diagnosed early.

While there’s always a risk that cancer may return after treatment (recur), most people who receive treatment in the early stages of the disease remain cancer-free.

### **What’s the survival rate for vulvar cancer?**

The relative five-year survival rate for people with vulvar cancer is approximately 70%. But survival rates are higher when people are diagnosed and treated in the early stages. For example, the five-year survival rate for localized cancer (remaining in the vulva) is approximately 86%. The five-year survival rate drops to approximately 30% once the cancer spreads.

Still, your prognosis depends on factors unique to your diagnosis, including your health and your response to treatment. Ask your healthcare provider about likely outcomes based on your diagnosis.

### **How quickly does vulvar cancer progress?**

Most types of vulvar cancer progress slowly over several years. Less common types, like melanomas, tend to grow and spread more quickly.

## **Prevention**

### **Can vulvar cancer be prevented?**

The best way to reduce your risk is to get the [HPV vaccine](https://my.clevelandclinic.org/health/treatments/21613-hpv-vaccine) to prevent infections. In the U.S., adults up to age 45 may receive Gardasil 9® depending on their risk of HPV exposure. Cervarix® and Gardasil® are HPV vaccines available in other countries.

See your healthcare provider right away if you develop any symptoms of vulvar cancer. Schedule regular checkups, including a [physical exam](https://my.clevelandclinic.org/health/diagnostics/17366-physical-examination), at least annually for your [gynecological health](https://health.clevelandclinic.org/well-woman-exam/).

## **Living With**

### **How do I take care of myself?**

Many people feel self-conscious about visible changes to their vulva. Still, having vulvar cancer doesn’t mean you must abandon physical intimacy. Don’t be ashamed to ask your healthcare provider how your diagnosis may affect your sex life. They can connect you with resources that support your physical and emotional needs as you navigate your diagnosis and treatment.

## **Additional Common Questions**

### **Where does vulvar cancer usually start?**

Vulvar cancer usually starts on the surface of the skin surrounding your vagina, either your outer lips (labia majora) or inner lips (labia minora). Less commonly, it forms on other parts of your vulva, like your Bartholin gland and clitoris.

### **What is the first stage of vulvar cancer?**

Stage I is the first stage of vulvar cancer. In this stage, cancer hasn’t spread beyond your vulva or perineum. Stage IA vulvar cancer is two centimeters (peanut size) or smaller. It hasn’t spread beyond one millimeter (tip of a pencil-size) into nearby tissue beyond one millimeter. Stage IB vulvar cancers involve larger tumors that may have invaded more deeply into nearby tissue.

[Vulvar Cancer: Symptoms, Causes & Treatment](https://my.clevelandclinic.org/health/diseases/6220-vulvar-cancer#overview)