JAMA | Review

Prostate Cancer
A Review

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IMPORTANCE Prostate cancer is the most common nonskin cancer in men in the US, with an estimated 299 010 new cases and 35 250 deaths in 2024. Prostate cancer is the second most common cancer in men worldwide, with 1 466 680 new cases and 396 792 deaths in 2022.

OBSERVATIONS The most common type of prostate cancer is adenocarcinoma (≥99%), and the median age at diagnosis is 67 years. More than 50% of prostate cancer risk is attributable to genetic factors; older age and Black race (annual incidence rate, 173.0 cases per 100 000 Black men vs 97.1 cases per 100 000 White men) are also strong risk factors. Recent guidelines encourage shared decision-making for prostate-specific antigen (PSA) screening. At diagnosis, approximately 75% of patients have cancer localized to the prostate, which is associated with a 5-year survival rate of nearly 100%. Based on risk stratification that incorporates life expectancy, tumor grade (Gleason score), tumor size, and PSA level, one-third of patients with localized prostate cancer are appropriate for active surveillance with serial PSA measurements, prostate biopsies, or magnetic resonance imaging, and initiation of treatment if the Gleason score or tumor stage increases. For patients with higher-risk disease, radiation therapy or radical prostatectomy are reasonable options; treatment decision-making should include consideration of adverse events and comorbidities. Despite definitive therapy, 2% to 56% of men with localized disease develop distant metastases, depending on tumor risk factors. At presentation, approximately 14% of patients have metastases to regional lymph nodes. An additional 10% of men have distant metastases that are associated with a 5-year survival rate of 37%. Treatment of metastatic prostate cancer primarily relies on androgen deprivation therapy, most commonly through medical castration with gonadotropin-releasing hormone agonists. For patients with newly diagnosed metastatic prostate cancer, the addition of androgen receptor pathway inhibitors (eg, darolutamide, abiraterone) improves survival. Use of abiraterone improved the median overall survival from 36.5 months to 53.3 months (hazard ratio, 0.66 [95% CI, 0.56-0.78]) compared with medical castration alone. Chemotherapy (docetaxel) may be considered, especially for patients with more extensive disease.

CONCLUSIONS AND RELEVANCE Approximately 1.5 million new cases of prostate cancer are diagnosed annually worldwide. Approximately 75% of patients present with cancer localized to the prostate, which is associated with a 5-year survival rate of nearly 100%. Management includes active surveillance, prostatectomy, or radiation therapy, depending on risk of progression. Approximately 10% of patients present with metastatic prostate cancer, which has a 5-year survival rate of 37%. First-line therapies for metastatic prostate cancer include androgen deprivation and novel androgen receptor pathway inhibitors, and chemotherapy for appropriate patients.

Multimedia

Supplemental content

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An estimated 299 010 new diagnoses of prostate cancer were made in the US in 2024.[1] Prostate cancer is heterogeneous and presentation ranges from an asymptomatic, screen-detected lesion that may never progress to an aggressive malignancy, representing a leading cause of morbidity and mortality worldwide.[2,3] Therefore, individualized strategies for screening and management of localized prostate cancer are needed to avoid overtreatment while also preventing progression to metastatic disease.

The most common type of prostate cancer is adenocarcinoma (≥99%).[4] Primary neuroendocrine prostate cancer, including small-cell prostate cancer, is rare[5] and will not be discussed further in this Review. Prostate adenocarcinomas are stimulated by androgen receptor signaling. Therefore, androgen deprivation therapy (ADT) is the primary treatment for patients with prostate cancer for whom systemic treatment is indicated.[6,7] Recent insights into the biology of prostate cancer have led to new diagnostic tools, such as prostate cancer–specific positron emission tomography (PET), and new therapeutic strategies, including more effective androgen receptor inhibition, cytotoxic chemotherapy, and cell surface antigen–targeted therapies. This Review summarizes current evidence regarding the epidemiology, diagnosis, and management of localized and metastatic prostate cancer. A summary of the risk factors and treatments for prostate cancer appears in the **Box**.

Box. Risk Factors and Treatments for Localized and Metastatic Prostate Cancer

What are the main risk factors for prostate cancer?
- Older age, genetic factors, and Black race are the strongest risk factors associated with the development of prostate cancer.
- Germline alterations in genes involved in DNA damage repair are found in 12% of patients with metastatic prostate cancer.

What is the most effective therapy for localized prostate cancer?
- Treatment of localized prostate cancer depends on risk stratification (defined by serum prostate-specific antigen level, clinical tumor staging based on digital rectal examination, and Gleason score or group), life expectancy, and personal preference.
- For many patients with low-risk or favorable intermediate-risk disease, active surveillance with serial prostate-specific antigen screenings, digital rectal examinations, prostate biopsies, and magnetic resonance imaging may be considered.
- Patients with higher-risk disease may be treated either with radical prostatectomy or radiation therapy.

What is first-line treatment for newly diagnosed metastatic prostate cancer?
- For most patients with newly diagnosed metastatic prostate cancer, androgen deprivation therapy with orchiectomy or a gonadotropin agonist or antagonist should be used.
- Treatment should also include androgen deprivation in combination with an androgen receptor pathway inhibitor (such as abiraterone or enzalutamide).
- The addition of chemotherapy (docetaxel) may be considered for some patients, especially those with more advanced disease.

Methods

A PubMed search was conducted to identify English-language articles describing observational studies, randomized clinical trials, meta-analyses, and systematic reviews of prostate cancer published between January 1, 2014, and December 11, 2024. A total of 401 randomized clinical trials, 203 meta-analyses, and 291 systematic reviews were identified. Randomized clinical trials were prioritized for inclusion. This Review includes a total of 114 articles (39 randomized clinical trials, 43 observational cohort studies, 9 meta-analyses, 9 systematic reviews, and 14 guideline recommendations), including publications prior to 2014.

Observations and Discussion

Epidemiology and Risk Factors

There were an estimated 3 399 229 men living with prostate cancer in the US in 2021.[1] Prostate cancer is the second most common cause of cancer and cancer death among men in the US, with an estimated 35 250 deaths in 2024.[1] Prostate cancer is also the second most common cause of cancer in men worldwide, with 1 466 680 new cases and 396 792 deaths in 2022.[2] Incidence varies, with the highest age-standardized rates observed in Northern Europe (82.8 per 100 000 person-years), Australia (78.1 per 100 000 person-years), the Caribbean (73.8 per 100 000 person-years), and North America (73.5 per 100 000 person-years), likely due to a combination of increased prostate-specific antigen (PSA) screening, life expectancy, genetics, and modifiable risk factors such as diet and obesity.[2,8]

Prostate cancer occurs predominantly in older men and the median age at diagnosis is 67 years (IQR not available).[1] Data from autopsy series show a nonlinear increase in cases of occult prostate cancer with advancing age; 59% of men older than 79 years had histological evidence of prostate cancer.[9,10] The annual incidence rate of prostate cancer is 173.0 cases per 100 000 Black men vs 97.1 per 100 000 White men and the mortality rate is 38.7 per 100 000 Black men per year vs 18.0 per 100 000 White men per year.[1] The reasons for the disparities in incidence and mortality are complex and not entirely understood. After accounting for differences in incidence, disparities in mortality persist and may reflect inequities in access to health care, the quality of care received, and presence of more aggressive cancer biology.[11-13]

Prostate cancer is highly hereditable. Results from twin studies performed in Northern Europe reported that more than 50% of prostate cancer risk is attributable to genetic factors.[14] A registry study conducted in Sweden, including 51 897 brothers of 32 807 men with prostate cancer, reported that men with a brother who had prostate cancer had a 14.9% (95% CI, 14.1%-15.8%) probability of having prostate cancer at 65 years of age and a 30.3% (95% CI, 29.3%-31.3%) probability at 75 years of age.[15]

A genome-wide association study[16] identified 451 genomic variants associated with risk for prostate cancer. A risk score based on these genomic variants stratified individuals effectively: 51.2% of prostate cancer cases occurred in the top quintile of risk vs 4.4% of cases in the bottom quintile. A germline analysis of 692 men with metastatic prostate cancer unselected for family cancer history identified 11.8% with a pathogenic alteration in a DNA repair gene, most commonly *BRCA2* (5.3%).[17] Guidelines from the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology recommend panel-based germline genetic testing for

Table 1. National Comprehensive Cancer Network Risk Stratification[a]

Risk category	Definition[b]	Life expectancy	Treatment options
Very low	Grade group 1, PSA level <10 ng/mL, <3 core biopsy samples positive for cancer, and ≤50% cancer cells in each core biopsy sample	≥10 y	Active surveillance
		<10 y	Observation
Low	Grade group 1, PSA level <10 ng/mL, and clinical cancer stage T1-T2a (nonpalpable tumor by rectal examination or involving less than half of the prostate)	≥10 y	Active surveillance preferred; RT or radical prostatectomy
		<10 y	Observation or RT
Favorable intermediate	≤1 Intermediate risk factor, grade group 1 or 2, and <50% of core biopsy samples positive for cancer	>10 y	Active surveillance; RT or radical prostatectomy with or without pelvic lymph node dissection
		<10 y	Observation preferred; RT
Unfavorable intermediate	2 or 3 Intermediate risk factors, grade group 3, and ≥50% of core biopsy samples positive for cancer	≥10 y	RT and ADT for 4-6 mo or radical prostatectomy and pelvic lymph node dissection
		<10 y	RT and ADT or observation
High	Clinical cancer stage T3a (extension through prostatic capsule, but no seminal vesicle involvement), grade group 4 or 5, or PSA level >20 ng/mL	>5 y or Symptomatic	RT and ADT or radical prostatectomy and pelvic lymph node dissection
		<5 y	RT, ADT, or observation
Very high	Clinical cancer stage T3b-T4 (seminal vesicle involvement and invasion of adjacent structures), primary grade group 5, and ≥2 high-risk features	>5 y or Symptomatic	RT and ADT along with abiraterone or radical prostatectomy and pelvic lymph node dissection
		<5 y	RT, ADT, or observation

Abbreviations: ADT, androgen deprivation therapy; PSA, prostate-specific antigen; RT, radiation therapy.

[a] Adapted from the National Comprehensive Cancer Network.[20]

[b] The Gleason grading system is used to evaluate the aggressiveness of prostate cancer cells based on the architectural pattern observed in a standard prostate biopsy using 10 to 12 core biopsy samples. Each core biopsy sample is given a Gleason grade; the grades range from 1 to 5. A higher grade is associated with more aggressive disease and a poorer prognosis. The intermediate risk factors are cancer stage T2b or T2c (palpable, unilateral, and without extension through the prostatic capsule), grade group 2 or 3, and a PSA level of 10 to 20 ng/mL.

all patients with high-risk localized or metastatic prostate cancer, regardless of family history, to inform cascade genetic testing of relatives and the use of precision therapies targeting these gene alterations.[18-20]

Screening

Screening for prostate cancer with digital rectal examination (DRE) is not recommended due to poor diagnostic accuracy. In a systematic review and meta-analysis[21] of 4 prospective cohort studies and 3 retrospective studies with 9241 patients who underwent DRE and prostate biopsy, the pooled sensitivity of DRE was 51% and the pooled specificity was 59%. Screening may be performed by measuring the serum concentration of PSA. A PSA level is specific to the prostate, but elevations can be observed in nonmalignant conditions such as benign prostatic hyperplasia and prostatitis.[22,23] Medications may affect PSA levels. For example, 5α-reductase inhibitors (such as finasteride) are associated with a 2-fold reduction in serum PSA levels in the 2 years after initiation and a 2.5-fold reduction thereafter.[24] The PSA level increases with age (0.04 ng/mL per year) due to increased prostate volume; therefore, age-specific reference ranges (eg, <2.5 ng/mL for men <50 years of age, <6.5 ng/mL for ages 70-79 years) should be considered when interpreting PSA values.[25] In a retrospective analysis of 4597 men who underwent radical prostatectomy for prostate cancer, use of age-specific PSA reference ranges increased detection of prostate cancer by 18% in men younger than 60 years. In older men, use of age-specific reference ranges reduced detection of prostate cancer by 22%[26]; however, 76% of the missed tumors had a very low risk or a low risk of pathological findings (**Table 1**).

Prostate cancer screening based on PSA level was widely adopted in the early 1990s.[27] However, when it became clear that detection of many prostate cancer cases with PSA screening did not result in decreased cancer-related morbidity or mortality, and that PSA screening led to biopsy-related and cancer treatment–related harms, randomized clinical trials were conducted to clarify the possible benefits of PSA screening (eTable in the Supplement).[3] The European Randomized Study of Screening for Prostate Cancer[28-30] demonstrated a modest reduction in prostate cancer mortality with PSA screening, but no improvement in quality-adjusted life-years. The US Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial[31-33] reported no mortality benefit, although this may have been due to substantial (approximately 90%) PSA testing prior to enrollment. A secondary analysis[34] of a cluster randomized clinical trial, including men aged 50 to 69 years from 573 primary care practices in England and Wales, reported a small reduction in prostate cancer mortality with PSA screening, but no effect on overall mortality. A systematic review and meta-analysis,[35] including these and 3 other PSA screening trials with 721 718 men, reported little or no effect on prostate cancer–specific mortality or all-cause mortality, but all included trials other than the European trial[28-30] had a high risk of bias.

Because the benefits of PSA screening are unclear, guidelines[36,37] encourage shared decision-making, incorporating the values and preferences of patients when making decisions about PSA testing. In 2018, the US Preventive Services Task Force[36] recommended shared decision-making for men aged 55 to 69 years, and no PSA screening beyond 70 years of age; this guideline is currently being updated. As of 2023, the American Urologic Association[37] recommends PSA screening every 2 to 4 years for men aged 50 to 69 years and provides adapted recommendations for screening in high-risk populations, such as Black men,[38] those with germline alterations in genes involved in DNA damage repair (particularly *BRCA1* or *BRCA2*), or those with a family history of prostate cancer. The Prostate Cancer Foundation[38] recommends Black men obtain information about PSA screening; among those who choose screening, baseline PSA testing should be performed between the ages of 40 and 45 years.

Clinical Manifestation and Presentation of Prostate Cancer

Among newly diagnosed cases of prostate cancer in the US, approximately 75% have localized disease (confined to the prostate) at presentation, 14% have metastases in regional lymph nodes, and 10% have distant metastases.[1] Cases of localized prostate cancer are rarely symptomatic. Lower urinary tract symptoms, such as urinary hesitancy and nocturia, are often described as symptoms of localized prostate cancer; however, a strong association has not been demonstrated.[39]

For patients with metastatic disease at presentation, bone is the most commonly involved site (observed in 82%), and may cause bone pain and fractures.[40] In a cohort study,[41] including 569 men with prostate cancer who presented with bone metastases, 43.6% had a skeletal-related event such as spinal cord compression or pathological fracture over a median follow-up of 2.2 years (IQR, 1.01-4.01 years). Metastasis to distant lymph nodes (34%) and visceral organs (5%) is less common.[40]

Diagnostic Evaluation

Among men with a new, moderately elevated PSA level (4-10 ng/mL), the PSA level decreases to the normal range in 25% to 40% of men when retested; therefore, a repeat PSA test to confirm elevation of PSA level should be performed, typically within a few months.[37,42] Patients with an elevated PSA level on repeat testing should be referred to a urologist for consideration of prostate biopsy, which may be performed transrectally or transperineally with ultrasound guidance. A recent randomized clinical trial,[43] including 718 patients, reported similar rates of infectious complications with transrectal vs transperineal approaches (2.6% vs 2.7%) and noninfectious complications (1.7% vs 2.2%, respectively), such as bleeding or urinary retention. The guidelines[44] from the American Urologic Association recommend that at least 10 to 12 core biopsy samples are taken symmetrically and include all areas of the prostate gland.

Pathological evaluation of prostate core biopsy samples is based on the Gleason grading system, which characterizes the architectural pattern of the tumor.[45] Each biopsy core is given a Gleason grade (range, 1-5) with pattern 1 most resembling normal prostate tissue and pattern 5 consisting of sheets of cells with few or no recognizable glands. The Gleason grades for the 2 most dominant patterns are added together, and the combined number is referred to as the Gleason score (range, 2-10). In 2014, an updated grading system[46] was developed that assigns a grade group from 1 to 5 on the basis of the Gleason score.

Magnetic resonance imaging (MRI) performed prior to biopsy may aid in the detection of clinically significant cancer (defined as a Gleason score ≥7). A noninferiority trial[47] randomized 1532 men with a PSA level of 3 ng/mL or greater to collection of the standard 10 to 12 core biopsy samples vs an experimental biopsy, in which patients underwent MRI followed by targeted and standard biopsy if the MRI was suggestive of prostate cancer (36% of patients in the experimental group underwent biopsies vs 73% in the standard care group). The rate of clinically significant cancer cases was 21% in the experimental biopsy group vs 18% in the standard biopsy group (between-group difference of 3% [95% CI, −1% to 7%]; $P < .001$ for noninferiority); fewer clinically insignificant cancers were detected (4% vs 12%, respectively; between-group difference of −8% [95% CI, −11% to −5]).[47] Long-term outcome data regarding benefit of MRI prior to biopsy are not yet available, and there is no consensus about which patients should undergo this testing.

Risk Stratification

To stratify patients into risk categories, physicians use the degree of PSA elevation, assessments of tumor size by DRE, and Gleason score and Gleason grade. Categorization differs slightly worldwide, but a commonly accepted risk stratification was proposed by the NCCN (Table 1).[19,20] Risk stratification provides information about risk for progression to metastatic, fatal disease and informs therapeutic decision-making. In the most recent nationally representative data available (from 2004 to 2014) in the US National Cancer Database, 34% of patients presented with low-risk cancer, 44% with intermediate-risk cancer, and 21% with high-risk cancer.[48]

Patients with unfavorable intermediate- or higher-risk disease should undergo staging based on a computed tomographic (CT) scan of the chest, abdomen, and pelvis and a radionuclide bone scan. However, a prostate-specific membrane antigen (PSMA) PET scan is increasingly used. Either approach (PET scan or CT and bone scans) is considered appropriate by the guidelines. A PSMA PET is a newer imaging technique, uses a radiotracer that binds to the PSMA protein on cells of prostatic origin, and has higher sensitivity and specificity compared with CT and bone scans.[49] A systematic review[50] of 18 studies, including 5 prospective observational trials with 969 patients who underwent PSMA PET imaging for primary lymph node staging using histopathology as the reference standard, reported a sensitivity of 59% and a specificity of 93% for the PSMA PET scan compared with a sensitivity of 42% and a specificity of 82% for CT and bone scans. However, PSMA PET imaging was not used in the trials studying the efficacy of current systemic or local therapies; therefore, caution is needed in translating PET imaging results to recommendations based on conventional imaging.

Treatment

Androgen Deprivation Therapy

Prostate adenocarcinoma is highly dependent on androgens (ie, testosterone and dihydrotestosterone) for growth.[51] Androgen deprivation therapy can be achieved surgically via orchiectomy or medically via administration of a gonadotropin-releasing hormone agonist (eg, leuprolide) or antagonist (eg, degarelix) with the goal of achieving a serum testosterone level of 50 ng/mL or less.[52] The benefit of ADT is best established in patients with high-risk localized disease undergoing radiation therapy (RT), in those with lymph node metastases detected after prostatectomy, and as palliative treatment in those with metastatic disease.[53,54]

However, ADT has substantial negative effects on quality of life, including erectile dysfunction (>70%), hot flashes (60%), gynecomastia (10%), and changes in body composition (a 9% increase in body fat).[55,56] The use of ADT is also associated with osteopenia, osteoporosis, and fracture. A retrospective study,[57] including 50 613 men with prostate cancer, reported a higher incidence of fracture in those who received ADT vs those who did not (19.4% vs 12.6%, respectively; $P < .001$). Patients receiving ADT who are at increased risk for fracture according to the Fracture Risk Assessment Tool should have bone mineral density assessed at baseline and every 1 to 2 years thereafter, and should be treated for osteoporosis based on guidelines from the Bone Health and Osteoporosis Foundation.[58,59] Use of ADT may also increase the risk for diabetes and cardiovascular disease. In an observational study,[60] including 73 196 patients with locoregional

prostate cancer, the patients who received a gonadotropin-releasing hormone agonist had higher incidence rates of diabetes compared with the patients who did not receive ADT (29.0 vs 20.9 cases per 1000 person-years, respectively; $P < .001$), myocardial infarction (13.5 vs 10.9 cases per 1000 person-years; $P < .001$), and sudden cardiac death (12.9 vs 9.0 cases per 1000 person-years; $P < .001$).

Prostate cancer that progresses despite ADT (termed *castration-resistant prostate cancer*) often continues to depend on activation of the androgen receptor, which may occur through production of androgens within the tumor or changes to the androgen receptor.[61,62] To target this ongoing androgen dependence, newer hormonal therapies (referred to as androgen receptor pathway inhibitors [ARPIs]) have been developed and include androgen receptor inhibitors (eg, enzalutamide, darolutamide, apalutamide) and inhibitors of androgen biosynthesis (abiraterone), which are used in a variety of contexts (**Figure 1**).

Management of Clinically Localized Disease

For patients presenting with localized prostate cancer, 5-year cancer-specific survival rates approach 100%.[1] These patients may be treated with curative-intent local therapy (eg, radiotherapy or surgery), active surveillance, or observation. Treatment choice is based on risk stratification (Table 1), patient preference, and life expectancy.

Use of active surveillance has increased substantially and continues to increase for men with newly diagnosed low-risk prostate cancer, and involves some combination of serial PSA tests, DRE, prostate biopsy, and MRI.[63] Patients who develop disease progression (eg, a reduction in the PSA doubling time, a change in DRE results, or a detection of higher-grade disease on prostate biopsy) are then considered for active intervention. This approach was studied in a multicenter, prospective, observational active surveillance study[64] including 2155 patients with low-risk disease who were followed up with PSA tests every 3 to 6 months and prostate biopsies at 6 to 12 months, at 24 months, and every 2 years thereafter. At 10 years after diagnosis, 49% of patients remained free of disease progression or treatment for prostate cancer, less than 2% developed metastases, and less than 1% died of prostate cancer.[64]

The guidelines recommend definitive local therapy with radical prostatectomy or RT for patients with intermediate-risk disease and a life expectancy of longer than 10 years or for patients with higher-risk disease and a life expectancy of longer than 5 years.[20,65] The decision between radical prostatectomy and RT is typically made based on the adverse effect profile of the treatment, patient comorbidities, and the ability of the patient to tolerate treatment. Ideally, treatment decisions are made in consultation with a multidisciplinary team consisting of a radiation oncologist, urologic oncologist, and medical oncologist.

Radical prostatectomy is associated with surgical risks, including blood loss requiring transfusion (3.6%) and urological infections (3.4%); complications leading to death or organ failure are rare (<1%).[66] Surgical experience is associated with lower surgical complication rates across retrospective studies.[67,68] The largest study, including 25 404 patients, reported that 50 patients (0.2%) died in the hospital after surgery; in-hospital mortality was lower at high-volume centers (odds ratio, 0.82; 95% CI, 0.69-0.99).[68] Radical prostatectomy is associated with the development of stress urinary incontinence (in approximately 15% of patients at 12 months) and erectile dysfunction (in 20%-60% of patients with rates dependent on presurgical function and surgical approach); however, prostatectomy can improve lower urinary tract symptoms, if present, and avoids the need for concurrent ADT, which is often recommended for patients with high-risk disease undergoing RT.[69-72] For men with lymph node–positive prostate cancer at prostatectomy, adjuvant ADT may be considered based on a trial[53] including 98 patients randomized to adjuvant ADT vs observation (median overall survival, 13.9 years vs 11.3 years; hazard ratio [HR], 1.84 [95% CI, 1.01-3.35]).

The use of RT may be preferable to surgery for older patients or those with comorbidities precluding surgery.[72] However, RT is associated with bowel toxicities such as rectal urgency, frequency, or hematochezia (11% of patients reported at least a moderate problem) as well as genitourinary toxicities such as irritation or obstruction (14% of patients reported at least a moderate problem).[72] The modalities of RT for localized prostate cancer include external-beam RT with or without implantation of radioactive seeds (brachytherapy). Brachytherapy alone can be used for patients with intermediate-risk disease, or as a boost to external-beam RT for those with high-risk disease (Table 1).[73] Patients with high-risk disease choosing RT should be offered concurrent ADT based on the survival benefit demonstrated across several studies based on disease volume,[54] including a study of 1554 patients and comparing 2 treatment lengths of ADT (overall 15-year survival rate of 27.1% for 4 months of ADT vs 29.8% for 24 months of ADT; HR, 0.88 [95% CI, 0.79-0.98]).

Management of Locally Advanced Disease

Patients with regional lymph node involvement (N1 disease) may also benefit from definitive local treatment. A retrospective study,[74] including 2967 patients with pelvic lymph node–positive prostate cancer, reported a survival advantage associated with local therapy (radical prostatectomy or RT) and ADT compared with ADT alone (overall 5-year survival rate of 78.8% vs 49.2%, respectively; HR, 0.31 [95% CI, 0.13-0.74]). The addition of the androgen biosynthesis inhibitor abiraterone may also be considered in patients with regional lymph node involvement, in patients meeting 2 of these 3 criteria (PSA level ≥40, tumor stage T3 or T4, or Gleason grade 4 or 5), and in patients who are receiving local RT based on data from a meta-analysis[75] including 1974 patients from 2 randomized clinical trials that reported improved 6-year metastasis-free survival (82% in patients receiving abiraterone and ADT vs 69% in patients receiving ADT alone; HR, 0.53 [95% CI, 0.44-0.64]).

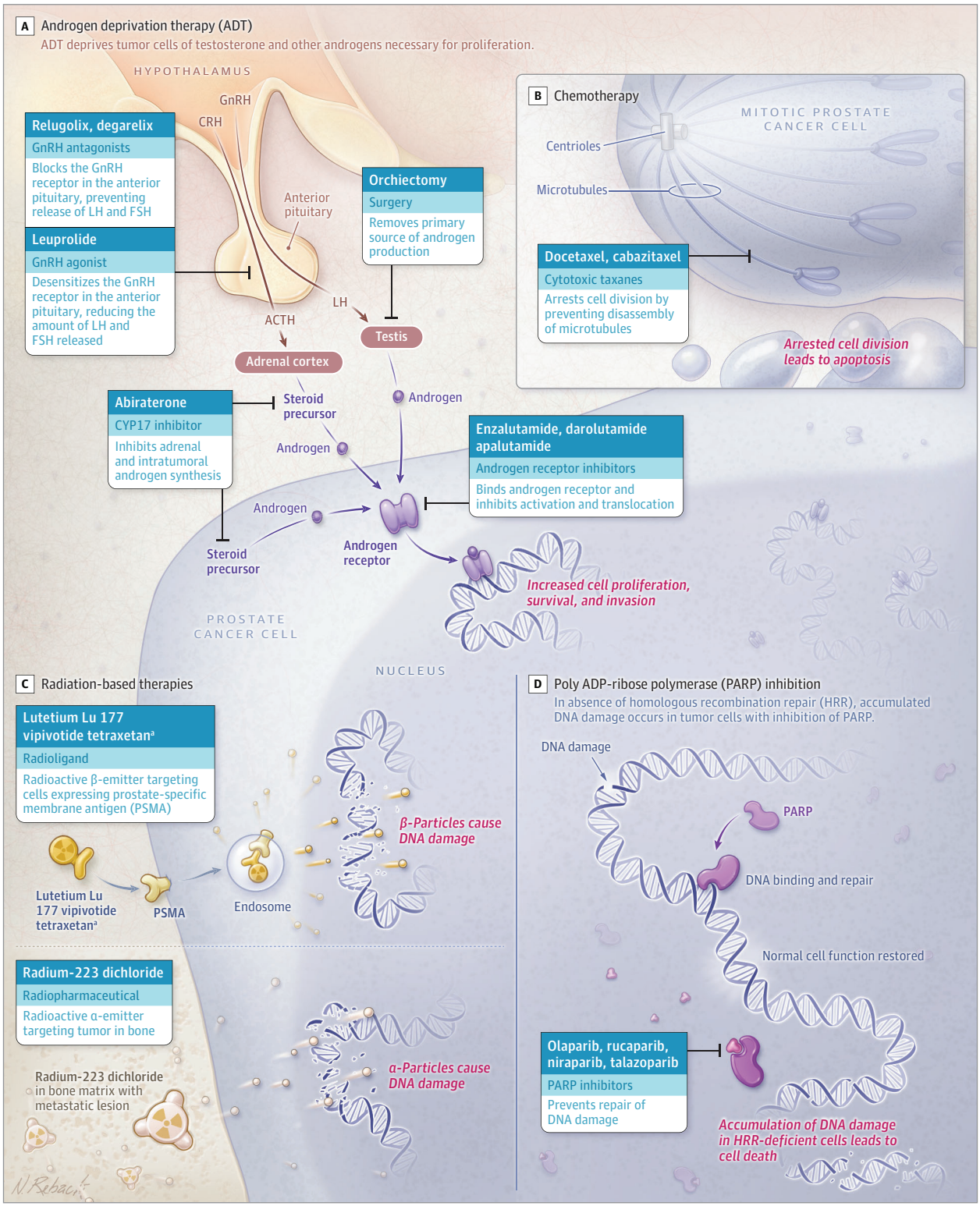
Surveillance After Definitive Local Therapy

Serial PSA measurement is the primary means of surveillance after patients receive definitive local therapy. The PSA level is typically monitored every 6 to 12 months for 5 years and then annually if there is no increase from the baseline PSA level. After prostatectomy, the PSA level should be checked at 6 weeks and should remain undetectable due to complete removal of the gland. A stable PSA level of 0.2 ng/mL or less may indicate retained benign prostate tissue; however, an elevation in PSA level greater than 0.2 ng/mL is considered recurrent prostate cancer. A higher PSA threshold of nadir PSA plus 2 ng/mL is used to define recurrence after RT because normal prostate tissue may remain after RT.[76]

Biochemical Recurrence

Biochemical recurrence, defined as an elevated PSA level as the sole indicator of recurrent disease, may occur in 20% to 40% of patients

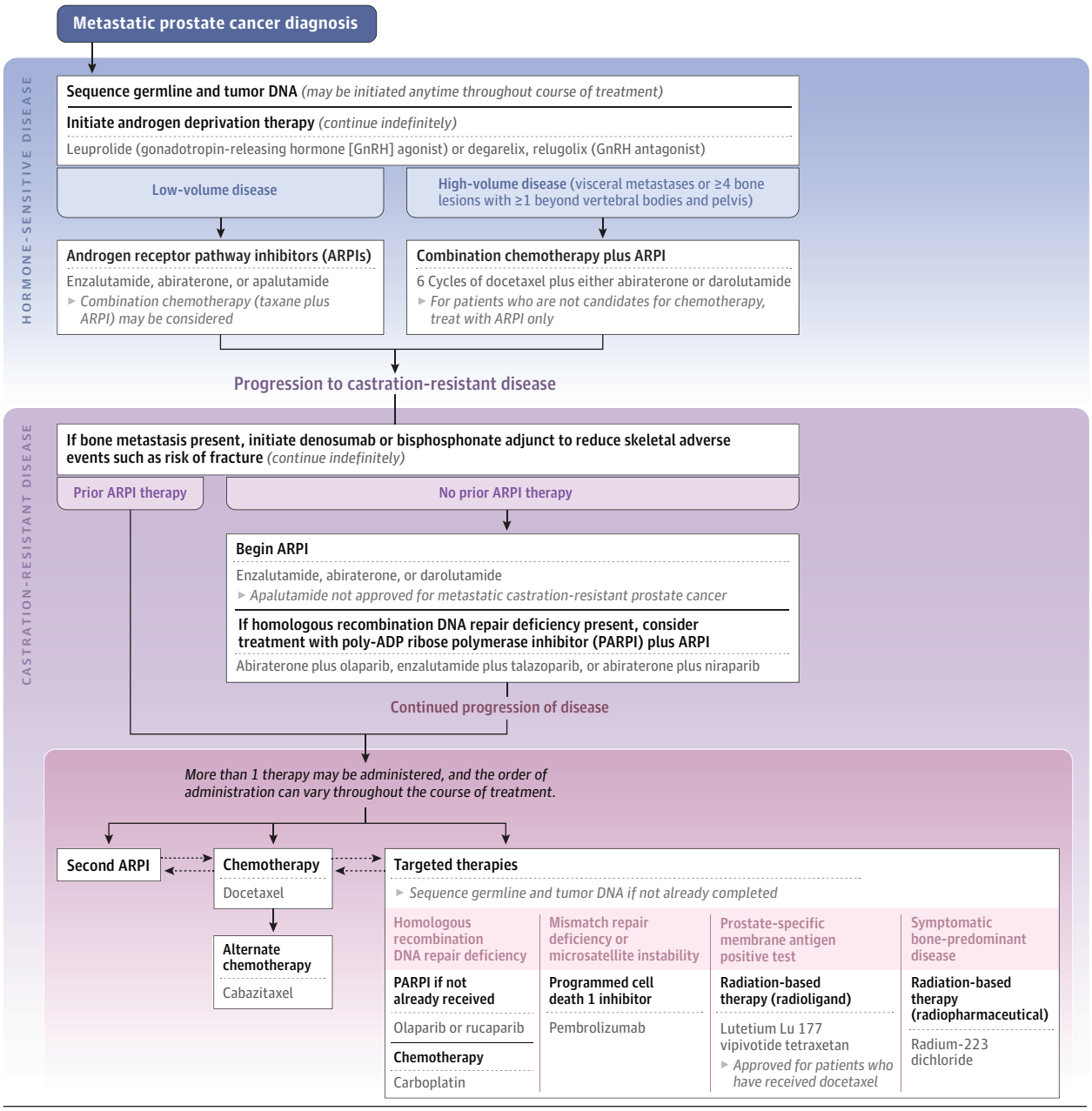
Figure 1. Mechanisms of Drugs Used for Systemic Therapy of Prostate Cancer



ACTH indicates adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

[a]Also called ^{177}Lu-PSMA-617.

Figure 2. Flowchart of Systemic Therapies for Metastatic Prostate Cancer



who undergo definitive therapy.[77-80] Salvage RT to the surgical bed may be used for individuals who have undergone radical prostatectomy and are experiencing biochemical recurrence. For individuals with biopsy-proven, recurrent, localized prostate cancer who initially received RT, salvage options of radical prostatectomy, cryotherapy, or other forms of ablative treatment (such as high-intensity-focused ultrasonography) may be considered.[81] The ideal timing for initiating ADT for individuals with biochemical recurrence who have undergone or are not candidates for salvage local therapy is uncertain and is an active area of study. A randomized clinical trial[82] assigned 1068 patients with high-risk biochemical recurrence (PSA doubling time ≤9 months) to enzalutamide plus leuprolide, enzalutamide alone, or leuprolide alone; combination treatment with enzalutamide and leuprolide improved metastasis-free survival compared with leuprolide alone (87.3% vs 71.4%, respectively; HR, 0.42 [95% CI, 0.30-0.61]). With more sensitive PSMA PET imaging, approximately 68% of patients who would previously have been considered as having biochemical recurrence are found to have metastatic disease.[83] The optimal management of these patients is unclear.

Metastatic Hormone-Sensitive Prostate Cancer

Approximately 10% of patients with prostate cancer present with de novo metastatic disease, and their 5-year survival rate is 37%.[1] In addition, despite definitive local therapy, metastatic disease develops in a substantial portion of men. Risk of metastasis correlates

Table 2. Selected Trials for Treatment of Metastatic Hormone-Sensitive Prostate Cancer

Trial[a]	Disease setting	Treatment groups[b]		No. of patients	Primary end point	Overall survival			Serious adverse events in the intervention group[c]	
		Intervention	Control			Median, mo	HR (95% CI)	*P* value	Category	Patients, %
STAMPEDE,[112] 2016	Metastatic hormone-sensitive prostate cancer	Docetaxel (every 3 wk) for 6 cycles	ADT	1776	Overall survival	81 vs 71	0.78 (0.66-0.93)	.006	Febrile neutropenia	15
									Neutropenia	12
									Gastrointestinal tract disorder	8
									General disorder (includes lethargy, fever, and asthenia)	7
									Respiratory disorder	5
									Cardiac disorder or neuropathy[d]	3
CHAARTED,[89] 2015	Metastatic hormone-sensitive prostate cancer	Docetaxel (every 3 wk) for 6 cycles	ADT	790	Overall survival	57.6 vs 44.0	0.61 (0.47-0.80)	<.001	Neutropenia	12
									Febrile neutropenia	6
									Fatigue	4
									Allergic reaction	2
GETUG-AFU 15,[113] 2013	Metastatic hormone-sensitive prostate cancer	Docetaxel (every 3 wk) for 9 cycles	ADT	385	Overall survival	58.9 vs 54.2	1.01 (0.75-1.36)	NR	Neutropenia	21
									Febrile neutropenia	3
									Abnormal liver function test results	2
LATITUDE,[84,85] 2017 and 2019	Metastatic hormone-sensitive prostate cancer	Abiraterone	ADT	1199	Overall survival and radiographically determined progression-free survival	53.3 vs 36.5	0.66 (0.56-0.78)	<.001	Hypertension	21
									Hypokalemia	11
									Abnormal liver function test results or hyperglycemia[d]	5
ARASENS,[93] 2022	Metastatic hormone-sensitive prostate cancer	Darolutamide and docetaxel	Docetaxel	1305	Overall survival	Not reached vs 48.9	0.68 (0.57-0.80)	<.001	Neutropenia	34
									Febrile neutropenia	8
									Hypertension	6
									Anemia	5
									Pneumonia, hyperglycemia, or abnormal liver function test results[d]	3
PEACE-1,[91] 2022	De novo metastatic hormone-sensitive prostate cancer	Abiraterone and docetaxel	Docetaxel	710	Overall survival and radiographically determined progression-free survival	68.4 vs 56.4	0.82 (0.69-0.99)	<.001	Hypertension	22
									Neutropenia	10
									Hepatotoxicity	6
									Febrile neutropenia	5

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; NR, not reported.

[a] This is a representative list of phase 3 trials that highlights different pharmacological mechanisms and disease settings, prioritizing more recent studies with the largest sample sizes.

[b] In all treatment groups, ADT was continued.

[c] Grade 3 toxicity or greater.

[d] To conserve row space, the categories with the same percentage of patients who experienced the adverse event were combined in 1 row (eg, 3% of patients experienced cardiac disorder and 3% experienced neuropathy).

Table 3. Selected Trials for Treatment of Metastatic Castration-Resistant Prostate Cancer

Trial	Disease setting	Treatment group		No. of patients	Primary end point	Overall survival[a]			Serious adverse events in the intervention group[b]	
		Intervention	Control			Median, mo	HR (95% CI)	*P* value	Category	Patients, %
PREVAIL,[98] 2020	Metastatic castration-resistant prostate cancer; naive to treatment with chemotherapy	Enzalutamide	Placebo	1382	Overall survival and radiographically determined progression-free survival	36 vs 31	0.83 (0.75-0.93)	<.001	Hypertension	9
									Fractures	5
									Major cardiovascular events or fatigue[c]	4
									Gastrointestinal tract event or fall[c]	2
COU-AA-301,[100] 2011	Metastatic castration-resistant prostate cancer; prior use of chemotherapy	Abiraterone	Placebo	1195	Overall survival	14.8 vs 10.9	0.65 (0.54-0.77)	<.001	Fatigue	8
									Anemia	7
									Back pain	6
									Hypokalemia or cardiac disorder[c]	3
CARD,[105] 2019	Metastatic castration-resistant prostate cancer; prior use of docetaxel	Cabazitaxel	Switch to alternative ARPI	255	Radiographically determined progression-free survival	13.6 vs 11.0	0.64 (0.46-0.89)	.008	Neutropenia	45
									Leukopenia	32
									Infection or anemia[c]	8
									Fatigue	4
									Peripheral neuropathy, kidney disorder, or increased level of AST[c]	3
IMPACT,[114] 2010	Metastatic castration-resistant prostate cancer	Sipuleucel-T (cellular immunotherapy)	Placebo	512	Overall survival	25.8 vs 21.7	0.77 (0.61-0.97)	.02	Back pain	4
									Arthralgia or asthenia[c]	2
									Chills or fatigue[c]	1
ALSYMPCA,[103] 2013	Metastatic castration-resistant prostate cancer; prior disease of bone only	Radium-223 dichloride	Placebo	921	Overall survival	14.9 vs 11.3	0.70 (0.58-0.83)	<.001	Bone pain	25
									Anemia	13
									Thrombocytopenia	7
									Fatigue	5
									Neutropenia	3
									Nausea, vomiting, anorexia, or pathological fracture[c]	2
VISION,[104] 2021	Metastatic castration-resistant prostate cancer; prior use of chemotherapy and treatment with an ARPI	Lutetium Lu 177 vipivotide tetraxetan[d]	Protocol-permitted standard of care	831	Overall survival and radiographically determined progression-free survival	15.3 vs 11.3	0.62 (0.52-0.74)	<.001	Anemia	13
									Thrombocytopenia or lymphopenia[c]	8
									Fatigue	6
									Leukopenia or back pain[c]	3
PROfound,[107] 2020	Metastatic castration-resistant prostate cancer; prior use of an ARPI and had an HRR[e] alteration	Olaparib	Switch to alternative ARPI	387	Radiographically determined progression-free survival	17.5 vs 14.3	0.67 (0.49-0.93)	NR	Anemia	21
									Fatigue	3
									Dyspnea or vomiting[c]	2

(continued)

Table 3. Selected Trials for Treatment of Metastatic Castration-Resistant Prostate Cancer (continued)

Trial	Disease setting	Treatment group		No. of patients	Primary end point	Overall survival[a]			Serious adverse events in the intervention group[b]	
		Intervention	Control			Median, mo	HR (95% CI)	*P* value	Category	Patients, %
TRITON3,[108] 2023	Metastatic castration-resistant prostate cancer; prior use of an ARPI and had a *BRCA1*, *BRCA2*, or *ATM* alteration	Rucaparib	Docetaxel or switch to another ARPI	405	Radiographically determined progression-free survival	10.2 vs 6.5	0.61 (0.47-0.80)	<.001	Anemia	24
									Fatigue or neutropenia[c]	7
									Thrombocytopenia	6
									Increased level of ALT or AST	5
									Nausea	3
PROpel,[80] 2023	Metastatic castration-resistant prostate cancer	Olaparib plus abiraterone	Abiraterone	1103	Radiographically determined progression-free survival	42.1 vs 34.7	0.81 (0.67-1.00)	.05	Anemia	16
									Thromboembolic event	8
									Hypertension	4
									Fatigue	3
									Neutropenia	2
MAGNITUDE,[110] 2023	Metastatic castration-resistant prostate cancer; had an HRR[e] alteration	Niraparib plus abiraterone	Abiraterone	423	Radiographically determined progression-free survival	16.5 vs 13.7	0.73 (0.56-0.96)	.02	Anemia	30
									Hypertension	15
									Thrombocytopenia or neutropenia[c]	7
									Fatigue or hypokalemia[c]	3
TALAPRO-2,[111] 2023	Metastatic castration-resistant prostate cancer; prior use of abiraterone allowed for castration-sensitive disease	Talazoparib plus enzalutamide	Enzalutamide	805	Radiographically determined progression-free survival	Not reached vs 21.9	0.63 (0.51-0.78)	<.001	Anemia	46
									Neutropenia	18
									Thrombocytopenia	7
									Leukopenia	6
									Hypertension	5
									Fatigue	4
									Back pain	3

Abbreviations: ALT, alanine aminotransferase; ARPI, androgen receptor pathway inhibitor; AST, aspartate aminotransferase; HR, hazard ratio; HRR, homologous recombination repairs; NR, not reported.

[a] For the MAGNITUDE and TALAPRO-2 studies, the outcome of overall survival was immature at the time of analysis.

[b] Grade 3 toxicity or greater.

[c] To conserve row space, the categories with the same percentage of patients who experienced the adverse event were combined in 1 row (eg, 4% of patients experienced major cardiovascular events and 4% experienced fatigue).

[d] Also called ^{177}Lu-PSMA-617.

[e] This is a component of the DNA damage repair pathway.

with Gleason grade as reported in a cohort study[45] including 581 patients with 17-year follow-up; 56% of patients with a Gleason grade of 5 developed metastatic disease compared with 2% of patients with a Gleason grade of 1.

Androgen deprivation therapy is the first-line treatment for metastatic prostate cancer, and is typically used indefinitely (**Figure 2**). Guidelines from the NCCN[20] recommend PSA testing every 3 to 6 months, with the addition of imaging based on increasing PSA level or symptoms. A reduction in PSA level by 50% is observed in 60% to 80% of patients treated with ADT alone; however, castration-resistant disease invariably develops, with a median time to progression of 12 to 24 months.[52,84] For most patients with metastatic hormone-sensitive prostate cancer, the NCCN guidelines[20] recommend use of ADT and an ARPI, with or without docetaxel chemotherapy. A trial,[85] including 1199 patients with newly diagnosed metastatic disease, reported an overall survival benefit for abiraterone plus ADT vs ADT alone (53.3 months vs 36.5 months; HR, 0.66 [95% CI, 0.56-0.78]). The ARPIs enzalutamide and apalutamide also improved overall survival in newly diagnosed patients with metastatic castration-sensitive prostate cancer compared with ADT alone (**Table 2**); all 3 agents (abiraterone, enzalutamide, and apalutamide) are appropriate for this population.[84-88]

The decision to use chemotherapy is based largely on disease volume, which was originally defined in a trial that randomized 790 patients to docetaxel plus ADT vs ADT alone.[89] Patients were stratified according to presence of high-volume disease (had visceral metastases or ≥4 bone lesions with ≥1 lesion located beyond the vertebral bodies and pelvis) or low-volume disease. Docetaxel improved the overall survival in patients with high-volume disease (51.2 months for docetaxel plus ADT vs 34.4 months for ADT alone; HR, 0.63 [95% CI, 0.59-0.89]), but not in patients with low-volume disease (63.5 months vs not reached, respectively; HR, 1.04 [95% CI, 0.70-1.55]).[90]

A randomized clinical trial,[91] including 710 patients with newly diagnosed metastatic prostate cancer, assigned patients to abiraterone and docetaxel vs docetaxel alone and reported an overall survival benefit with ADT, docetaxel, and abiraterone (5.7 years vs 4.7 years; HR, 0.82 [95% CI, 0.69-0.98]). Another trial,[92,93] including 1305 patients (77% with high-volume disease), reported survival benefit with the ARPI darolutamide combined with docetaxel vs docetaxel alone (median survival, not reached vs 4.1 years; HR, 0.68 [95% CI, 0.57-0.80]), and observed benefits across the high- and low-volume subgroups.

Even though triple therapy with an ARPI, ADT, and docetaxel appears superior to ADT and docetaxel for patients with newly diagnosed metastatic prostate cancer, it is unknown whether the combination is superior to ADT and an ARPI. Therefore, ADT with an ARPI remains an appropriate, guideline-recommended choice for patients presenting with newly diagnosed metastatic hormone-sensitive prostate cancer.[20,94] Triple therapy is also a reasonable option, especially for patients with high-volume metastatic disease, and this regimen is also recommended by the guidelines from the NCCN.[20]

Metastatic Castration-Resistant Prostate Cancer

Despite treatment, all patients with metastatic disease eventually develop castration-resistant prostate cancer. Treatment for castration-resistant prostate cancer is determined by use of prior therapies (**Table 3**).[62] For patients previously treated with ADT alone, both docetaxel and ARPIs have demonstrated survival benefits.[95-98] The ARPIs enzalutamide and abiraterone are approved for individuals with or without prior docetaxel exposure.[99,100] For patients with prior use of an ARPI, switching to a different class (eg, from abiraterone to enzalutamide) can be considered; however, the likelihood of achieving a response is low (15%-30%), and this strategy should generally not be pursued in symptomatic patients.[101,102]

Two radiopharmaceutical agents have been approved by the US Food and Drug Administration for treating patients with castration-resistant prostate cancer who have received ARPIs and taxane chemotherapy. A trial,[103] including 921 patients with prostate cancer and bone metastases without visceral disease, reported an overall survival of 14.0 months for radium-223 dichloride compared with 11.2 months for placebo (HR, 0.70 [95% CI, 0.58-0.83]). For patients with PSMA-expressing castration-resistant prostate cancer, another trial[104] including 831 patients demonstrated overall survival of 15.3 months with the β-emitting PSMA-targeted radioligand lutetium Lu 177 vipivotide tetraxetan (also called ^{177}Lu-PSMA-617) compared with 11.3 months for protocol-permitted standard of care (HR, 0.62 [95% CI, 0.52-0.74]). A trial of 255 patients with castration-resistant prostate cancer previously treated with docetaxel reported a median survival of 13.6 months with cabazitaxel vs 11.0 months in those who switched to another ARPI (HR, 0.64 [95% CI, 0.46-0.89]).[105] For castration-resistant prostate cancer, the specific sequence of therapies has not been systemically studied; multiple strategies are appropriate.[20]

Genetic sequencing of tumor tissue is recommended by guidelines for all patients with castration-resistant prostate cancer.[19,20] Approximately 20% of patients with metastatic prostate cancer have an alteration in genes involved in DNA repair.[106] For this population, poly-ADP ribose polymerase (PARP) inhibitors (eg, rucaparib or olaparib) can be effective. A randomized clinical trial, including 405 patients with castration-resistant prostate cancer who had DNA repair pathogenic alterations (*BRCA1, BRCA2,* and *ATM)*, reported overall survival of 10.2 months for rucaparib vs 6.5 months for docetaxel or a change in ARPI (HR, 0.67 [95% CI, 0.49-0.93]).[107,108] For patients with DNA repair pathogenic alterations who have not received an ARPI, the combination of PARP inhibitors with ARPIs is currently approved; however, it is unknown whether this combination treatment is superior to the use of the agents in sequence.[109-111]

Limitations

This review has several limitations. First, some relevant studies may have been missed. Second, the quality of included studies was not formally reviewed. Third, some aspects of the epidemiology, diagnosis, and management of prostate cancer may have been excluded due to space limitations.

Conclusions

Approximately 1.5 million new cases of prostate cancer are diagnosed annually worldwide. Approximately 75% of patients present with cancer localized to the prostate, which is associated with a 5-year survival rate of nearly 100%. Management includes active surveillance, prostatectomy, or RT, depending on risk of progression. Approximately 10% of patients present with metastatic prostate cancer, which has a 5-year survival rate of 37%. First-line therapies for metastatic prostate cancer include androgen deprivation and novel ARPIs, and chemotherapy for appropriate patients.

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