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The Diagnosis and Treatment of Prostate Cancer
A Review

Mark S. Litwin, MD, MPH; Hung-Jui Tan, MD, MSHPM

IMPORTANCE Prostate cancer is the most common cancer diagnosis made in men with more than 160 000 new cases each year in the United States. Although it often has an indolent course, prostate cancer remains the third-leading cause of cancer death in men.

OBSERVATIONS When prostate cancer is suspected, tissue biopsy remains the standard of care for diagnosis. However, the identification and characterization of the disease have become increasingly precise through improved risk stratification and advances in magnetic resonance and functional imaging, as well as from the emergence of biomarkers. Multiple management options now exist for men diagnosed with prostate cancer. Active surveillance (the serial monitoring for disease progression with the intent to cure) appears to be safe and has become the preferred approach for men with less-aggressive prostate cancer, particularly those with a prostate-specific antigen level of less than 10 ng/mL and Gleason score 3 + 3 tumors. Surgery and radiation continue to be curative treatments for localized disease but have adverse effects such as urinary symptoms and sexual dysfunction that can negatively affect quality of life. For metastatic disease, chemotherapy as initial treatment now appears to extend survival compared with androgen deprivation therapy alone. New vaccines, hormonal therapeutics, and bone-targeting agents have demonstrated efficacy in men with metastatic prostate cancer resistant to traditional hormonal therapy.

CONCLUSIONS AND RELEVANCE Advances in the diagnosis and treatment of prostate cancer have improved the ability to stratify patients by risk and allowed clinicians to recommend therapy based on cancer prognosis and patient preference. Initial treatment with chemotherapy can improve survival compared with androgen deprivation therapy. Abiraterone, enzalutamide, and other agents can improve outcomes in men with metastatic prostate cancer resistant to traditional hormonal therapy.

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Author Affiliations: Department of Urology, David Geffen School of Medicine, University of California, Los Angeles (Litwin); Department of Health Policy and Management, Fielding School of Public Health, University of California, Los Angeles (Litwin); School of Nursing, University of California, Los Angeles (Litwin); Department of Urology, University of North Carolina, Chapel Hill (Tan).

Corresponding Author: Mark S. Litwin, MD, MPH, Department of Urology, University of California, 300 Stein Plaza, Third Floor, Los Angeles, CA 90095 (mlitwin@mednet.ucla.edu).

Section Editors: Edward Livingston, MD, Deputy Editor, and Mary McGrae McDermott, MD, Senior Editor.

Prostate cancer is the most common, noncutaneous cancer in men in the United States. In 2017, approximately 160 000 men will be diagnosed with prostate cancer, adding to 3.3 million existing survivors.[1,2] Although prostate cancer is common, the indolent course of many tumors and the potential for adverse treatment effects have generated controversy regarding the utility of screening and early detection.[3,4] Even so, prostate cancer can threaten long-term health and remains the third-leading cause of cancer death in men.[2] Since 2011, meaningful progress has been made in characterizing disease risk and identifying therapeutic options. This review summarizes advances in prostate cancer diagnosis and treatment. Screening for prostate cancer has been reviewed elsewhere.[5,6]

Methods

This search identified key articles by applying the Cochrane Highly Sensitive Search Strategy for randomized clinical trials, a string for meta-analyses and systematic reviews, and established Medical Subject Headings for prostate cancer diagnosis and treatment to the PubMed and Cochrane Databases from January 1, 2011, through March 31, 2017 (additional details appear in the eAppendix in the Supplement). Reviewing the references of screened articles identified additional observational studies. The authors then selected articles with consideration given to the general medical readership.

Advances in Diagnosis

Risk Stratification

The diagnosis of prostate cancer is based on the microscopic evaluation of prostate tissue obtained via needle biopsy. By convention, a systematic prostate biopsy is performed using transrectal ultrasound to obtain 10 to 12 tissue samples in a grid-like pattern. A pathologist examines these samples and issues a primary Gleason grade for the predominant histological pattern and a secondary grade for the highest pattern, both on a scale of 1 to 5 based on the microscopic architecture and appearance of the cells. Clinicians

have traditionally stratified the diagnosis into low, intermediate, and high risk based on the sum of Gleason patterns, prostate-specific antigen (PSA) level, and clinical stage. Because heterogeneity exists within each risk group, more discriminatory tools have been developed and validated (**Box**).[7-14] For example, the updated National Comprehensive Cancer Network risk stratification uses a 5-tier system that subdivides the low- and high-risk groups.[7]

In 2014, a consensus conference revised pathological grading into 5 strata.[13,14] This new framework incorporates 2 major changes. First, it recalibrates the grading scale by designating Gleason score 3 + 3 disease to grade 1 cancer. Second, it more precisely matches tumor behavior by differentiating between a Gleason score of 3 + 4 (grade 2) and a Gleason score of 4 + 3 (grade 3) and between Gleason scores of 4 + 4, 3 + 5, and 5 + 3 (grade 4) and Gleason scores of 4 + 5, 5 + 4, and 5 + 5 (grade 5). In a validation study of more than 25 000 men, this system offered the highest prognostic discrimination, increasing the C statistic by 0.02 to 0.05 over the traditional 3-tier system (ie, Gleason score of 6, Gleason score of 7, and Gleason scores of 8-10).[14] This new grading system was incorporated into the 2016 World Health Organization classification of tumors, which serves as the international standard for pathologists.[13]

Diagnostic Performance of Prostate Biopsy

Risk stratification depends on an accurate prostate biopsy. Even though systematic prostate biopsy (ultrasound-guided biopsy following a specified grid pattern of biopsies) remains the standard of care, this approach misses 21% to 28% of prostate cancers and undergrades 14% to 17%.[15] There are several new biomarkers (eg, 4Kscore, Prostate Health Index, prostate cancer antigen 3 test, ConfirmMDx) that help identify potential false-negative results.

Tests for serum PSA variants estimate the probability of prostate cancer in patients with a previous negative biopsy.[16,17] The prostate cancer antigen 3 test is performed using urine collected after prostatic massage and has been validated in this population, demonstrating an 88% negative predictive value for subsequent biopsy.[18] In other words, 88% of patients with a normal prostate cancer antigen 3 test have a negative subsequent prostate biopsy. An epigenetic assay applied to prostate biopsy tissue quantifies DNA methylation and offers similar discriminatory power.[19]

New imaging technology also has been adapted to enhance diagnostic performance. The most notable has been multiparametric magnetic resonance imaging (MRI), which uses a specialized phase (eg, diffusion-weighted, dynamic contrast–enhanced imaging) in addition to T2-weighted imaging.[20] When standardized scoring and reporting criteria (ie, Prostate Imaging Reporting and Data System version 2; collaboration of the American College of Radiology, European Society of Uroradiology, and AdMetech Foundation) are applied, MRI demonstrates a pooled sensitivity of 89% and a specificity of 73% for identifying prostate cancer.[21] Targeted biopsies of suspicious lesions can then be obtained through 3 approaches: (1) MRI image fusion with transrectal ultrasound using computerized software; (2) in-bore percutaneous biopsy during the actual MRI; and (3) visual review of the MRI with sequential prostate biopsy using transrectal ultrasound (ie, cognitive biopsy).

A prospective study of 1003 men who had undergone prostate biopsy found that targeted prostate biopsy using the MRI-ultrasound fusion vs systematic prostate biopsy identified 30% more cases of Gleason score ≥4 + 3 disease (173 vs 122, respectively; $P < .001$) and 17% fewer cases of Gleason score 3 + 3 or low-volume Gleason score 3 + 4 disease (213 vs 258; $P < .001$). Targeted prostate biopsy also outperformed the combination of targeted and systematic prostate biopsy for detecting high-volume Gleason score 3 + 4 or higher disease (area under the curve, 0.72 vs 0.67, respectively; $P < .05$).[22] In another prospective study of 1042 men, 16% of those with a negative MRI had Gleason score 3 + 4 or higher disease on systematic prostate biopsy, which would be missed by a target-only approach.[23] Additional questions regarding optimal indications, technical parameters, and reader or operator experience necessitate ongoing study and quality assurance.[24]

Key Points

Question What are the optimal methods for the diagnosis and treatment of prostate cancer based on current evidence?

Findings Improved risk classification methods, imaging techniques, and biomarkers have improved the ability to provide prognostic information to patients with prostate cancer. For the treatment of prostate cancer, monitoring for disease progression followed by local therapy is an accepted strategy for some men. Surgery and radiation techniques continue to evolve as treatment-related adverse effects are better defined. Median survival also has improved for men with metastatic disease and is now 5 years, due to the early administration of docetaxel and new drugs such as abiraterone, enzalutamide, and other agents.

Meaning With recent advances, prostate cancer can be accurately characterized and more optimally managed according to tumor biology, patient preferences, and survivorship goals.

Prognostic Molecular and Image-Based Biomarkers

New molecular biomarkers (eg, Decipher, Prolaris, Oncotype DX) that classify tumor aggressiveness have become available. Using biopsy tissue, a cell cycle progression score based on 31 genes can predict clinical progression (hazard ratio [HR], 1.63; 95% CI, 1.44-1.85) and prostate cancer mortality (HR, 2.09; 95% CI, 1.38-3.16).[25] A 17-gene assay applied to biopsy tissue can predict the risk of adverse pathology at prostatectomy (odds ratio, 2.1; 95% CI, 1.4-3.2), biochemical recurrence, and metastases.[26] A 22-marker genomic classifier test developed to quantify metastatic risk based on the prostatectomy specimen also provides prognostic information.[27] These and other molecular biomarkers may help identify indolent disease graded as Gleason score 3 + 4 or aggressive tumors diagnosed on biopsy as Gleason score 3 + 3. These methods provide potentially helpful prognostic information.

Similarly, MRI results may have prognostic value in certain clinical scenarios. More than 80% of MRI lesions with high scores from the Prostate Imaging Reporting and Data System contain clinically significant disease.[21] Conversely, a negative MRI carried a negative predictive value of 84% in a large prospective study.[23] Applied clinically, MRI results may offer guidance for men not receiving therapy who are undergoing monitoring for progression. In a retrospective study of 113 men with very low–risk prostate cancer (ie, Gleason score of 3 + 3, ≤2 positive biopsy cores, ≤50% involvement of any biopsy core), those with negative or low-suspicion MRI lesions had a rate of 24% to 29% for higher-grade cancer on repeat biopsy compared with 45% to 100% in men with

Box. Risk Stratification Schema for Prostate Cancer

National Comprehensive Cancer Network Risk Stratification[7]

Very low risk
Clinical stage of T1c, Gleason score of 6 or less, prostate-specific antigen (PSA) level of less than 10 ng/mL, less than 3 biopsy cores with cancer presence of 50% or less in each core, and PSA density of less than 0.15 ng/mL/g

Low risk
Clinical stage of T1 to T2a, Gleason score of 6 or less, and PSA level of less than 10 ng/mL

Intermediate risk
Clinical stage of T2b to T2c, Gleason score of 7, or PSA level of 10 to 20 ng/mL

High risk
Clinical stage of T3a, Gleason score of 8 to 10, or PSA level greater than 20 ng/mL

Very high risk
Clinical stage of T3b to T4, primary Gleason pattern 5, or greater than 4 biopsy cores with Gleason score of 8 to 10

Prostate Cancer Nomograms[8-11]

Calculates probability (0%-100%) of extent of disease, biochemical recurrence, cancer-specific survival based on age, PSA level, clinical stage, Gleason score, percentage of biopsy cores involved with cancer[a]

Cancer of the Prostate Risk Assessment[12]

Scoring system from 0 to 10 based on age, PSA level, Gleason pattern 4 or 5, clinical stage, percentage of biopsy cores involved with cancer

Low risk score: 0-2

Intermediate risk score: 3-5

High risk score: 6-10

Pathologic Grading System of the International Society of Urological Pathology[13,14]

Grade 1 cancer: Gleason score of 3 + 3
Only individual, discrete, well-formed glands

Grade 2 cancer: Gleason score of 3 + 4
Predominantly well-formed glands with lesser component of poorly formed, fused, or cribiform glands

Grade 3 cancer: Gleason score of 4 + 3
Predominantly poorly formed, fused, or cribiform glands with lesser component of well-formed glands

Grade 4 cancer: Gleason scores of 4 + 4, 3 + 5, and 5 + 3
Only poorly formed, fused, or cribiform glands or well-formed glands plus area lacking glands

Grade 5 cancer: Gleason scores of 4 + 5, 5 + 4, and 5 + 5
Lacks gland formation (or with necrosis) with or without poorly formed, fused, or cribiform glands

[a] More information is available at http://www.nomograms.org.

suspicious MRI lesions.[28] The clinical utility of molecular and image-based biomarkers remains an area of active investigation, especially with concurrent updates to pathological risk stratification and prostate cancer treatment.

Updates in Prostate Cancer Staging

Despite their limitations, ^{99m}technetium methylene diphosphonate bone scan and cross-sectional body imaging with computed tomography (CT) or MRI continue to be recommended for men at risk of metastases (eg, clinical stage T3-T4 disease in which the tumor extends beyond the capsule, PSA level >20 ng/mL, or >10% risk of lymph node involvement) and may be considered for those with evidence of possible recurrence (ie, PSA level >0.2 ng/mL after prostatectomy or increase of 2 ng/mL above nadir after radiation).[7,29]

Interest has grown in molecular or functional imaging with positron emission tomography (PET). Multiple radiotracers demonstrate activity in prostate cancer and 3 have received approval from the US Food and Drug Administration (FDA).[13,30] C-choline PET-CT has variable sensitivity (38%-98%) and specificity (50%-100%) depending on disease site (ie, local, nodal, distant) and PSA level. ^{18}F-fluciclovine PET-CT provides 89% to 100% sensitivity and 67% specificity for recurrent or metastatic prostate cancer and appears to have a better balance between sensitivity and specificity than ^{11}C-choline PET-CT. ^{18}F-sodium fluoride PET-CT has a sensitivity of 87% to 89% and a specificity of 80% to 91% but is limited to bony metastases. Beyond these approved agents, use of PET-CT and PET-MRI based on prostate-specific membrane antigen (an enzyme overexpressed in prostate cancer cells) compares favorably with existing modalities (sensitivity of 63%-92%; specificity of 88%-100%), particularly in patients with low PSA levels and for detection of regional lymph node metastases.

Advances in Treatment

Competing Risks and Shared Decision Making

Treatment has traditionally been considered in the context of life expectancy and risk of death from other causes. As reported in several randomized clinical trials, the risk of death from other causes supersedes the risk of death from prostate cancer.[31,32] From data collected in the Prostate Cancer Outcomes Study (a US, prospective cohort of men with localized prostate cancer),[33] the risk of death from other causes can be modeled as a function of comorbidity and age. The 10-year risk of death from prostate cancer ranged from 3% to 18% depending on the risk category, whereas men with any comorbidity had a 10-year mortality rate from other causes of 33% or higher.[33]

Patient preferences and values have begun to play an increasingly central role in medical decision making. Already endorsed for prostate cancer screening by at least 1 organization,[34] shared decision making involves a collaborative process in which patients and clinicians make decisions together. To date, several interventions that include written material, in-person counseling, and web-based tools have been investigated. Although a meta-analysis of 14 randomized clinical trials investigating shared decision-making aids revealed only a negligible association with health outcomes,[35] more recent trials demonstrate improved decision making and treatment selection, suggesting an emerging role for shared decision making.

Treatment for Localized Prostate Cancer

Men diagnosed with localized disease (defined as no identifiable regional lymph nodes or distant metastases) have 3 primary options: expectant management, surgery, and radiation. Expectant management (monitoring for prostate cancer progression while not undergoing definitive therapy) consists of watchful waiting and

Table 1. Protocols and Outcomes of Selected Active Surveillance Cohorts for Prostate Cancer[a]

	University of Toronto	University of California, San Francisco	Johns Hopkins University	Göteborg Screening Trial	ProtecT Active Monitoring Group
Source	Klotz et al,[37] 2015	Welty et al,[38] 2015	Tosoian et al,[39] 2015	Godtman et al,[40] 2016	Hamdy et al,[41] 2016
No. of participants	993	810	1298	474	545
Median follow-up, mo	77	60	60	96	120
Entry criteria	From 1995-1999: Gleason score ≤6 and PSA level ≤10 ng/mL; Gleason score ≤3 + 4 and PSA level ≤15 ng/mL if age >70 y Since 2000: Gleason score ≤6 and PSA level ≤10 ng/mL; Gleason score ≤3 + 4 and PSA level 10-20 ng/mL if life expectancy <10 y	Strict criteria: Gleason score ≤6, PSA level ≤10 ng/mL, clinical stage ≤T2c, ≤33% of positive biopsy cores, and ≤50% cancer in each biopsy core Also selected patients who do not meet strict criteria	Very low risk: Gleason score ≤6, PSA density <0.15 ng/mL,[2] clinical stage ≤T1c, ≤2 of positive biopsy cores, and ≤50% cancer in each biopsy core For older men: Gleason score ≤6, clinical stage ≤T2a, and PSA level <10 ng/mL	Prostate cancer diagnosed by PSA screening, Gleason score ≤7, PSA level <20 ng/mL, and clinical stage ≤T2c (78% had Gleason score of 6, clinical stage of T1, and PSA level <10 ng/mL)	Prostate cancer diagnosed by PSA screening, PSA level <20 ng/mL, and clinically localized disease (77% had Gleason score of 6, 90% had PSA level ≤10 ng/mL, and 75% had clinical stage of T1c)
Monitoring protocol	PSA test every 3 mo for 2 y and then every 6 mo, prostate biopsy within 1 y and then every 3-4 y until age 80 y	PSA test every 3 mo, transrectal ultrasound every 6 mo, prostate biopsy within 1 y and then every 1-2 y thereafter	PSA test or digital rectal examination every 6 mo, prostate biopsy annually	PSA test and clinical examination every 3-6 mo (every 12 mo in older men), prostate biopsy if cancer <2 mm and then when progression suspected or every 2-3 y	PSA test every 3 mo for 1 y and then every 6-12 mo, repeat prostate biopsy not required
Treatment threshold	PSA doubling time <3 y until 2008, biopsy reclassification, clinical progression	Primary biopsy reclassification, secondary anxiety, CAPRA risk reclassification, or clinical progression	Biopsy reclassification	PSA progression, biopsy reclassification, clinical progression	Increase of 50% in PSA triggered a review of treatment
Surveillance outcomes, No. (%)					
Definitive treatment	267 (27)	348 (43)	471 (36)	202 (43)	291 (53)
Metastasis	28 (2.82)	1 (0.12)	5 (0.40)	7 (1.48)	33 (6.06)
Prostate cancer mortality	15 (1.51)	0	2 (0.15)	6 (1.27)	8 (1.47)

Abbreviations: CAPRA, Cancer of the Prostate Risk Assessment; ProtecT, Prostate Testing for Cancer and Treatment; PSA, prostate-specific antigen.

[a] Active surveillance is an expectant management approach that monitors for prostate cancer progression and triggers treatment with the intent to cure.

active surveillance.[36] Watchful waiting consists of treating symptoms with palliative intent, whereas active surveillance involves a series of PSA testing, physical examinations, prostate biopsies, or a combination of these to monitor for progression with an intent to cure those who develop significant disease. Several cohort studies support the utility of this approach, finding the risk of metastasis and prostate cancer mortality to range from 0% to 6.1% in selected patients (**Table 1**).[37-41] For example, the study by Tosoian et al[39] of 1298 men with mostly very low–risk disease followed up for 60 months found metastasis in 5 men (0.4%) and death from prostate cancer in 2 men (0.15%).

The Prostate Testing for Cancer and Treatment (ProtecT) trial randomized 1643 men in the United Kingdom who had been screened for localized prostate cancer to active monitoring (n = 545), surgery (n = 553), or radiation (n = 545). In this study, active monitoring involved serial PSA testing with consideration of treatment following a 50% increase in PSA level without requirement for repeat biopsy. At 120 months, ProtecT found that 8 of 545 men (1.5%) on active monitoring died from prostate cancer, which did not differ significantly from the 5 deaths (0.9%) after surgery or the 4 deaths (0.7%) after radiation.[41] Even though half of the men in active monitoring ultimately received treatment, this group maintained better quality of life.[42] As the optimal surveillance strategy continues to be debated, these findings provide support for active surveillance as the preferred choice for men with low-risk disease.[7,36,43]

Surgery and radiation continue to be effective treatments for men with more significant cancer, such as those with a PSA level greater than 10 ng/mL and those with nodules palpable on digital rectal examination. **Table 2** provides details on 3 randomized clinical trials comparing surgery, radiation therapy, and expectant management approaches. The Prostate Cancer Intervention versus Observation Trial (PIVOT) randomized 731 men at the Veterans Affairs Health System and National Cancer Institute sites to radical prostatectomy or watchful waiting, albeit with multiple methodological limitations that include incomplete accrual and an unhealthy study population. Even though no significant difference in prostate cancer or all-cause mortality overall was found in PIVOT, men with a PSA level greater than 10 ng/mL had better all-cause (48.4% vs 61.6%, respectively; $P = .02$) and prostate cancer-specific (5.6% vs 12.8%; $P = .02$) mortality following surgery.[31]

The Scandinavian Prostate Cancer Group Study 4 randomized 695 men to surgery vs watchful waiting, 76% of whom had a palpable tumor (ie, clinical stage ≥T2). Updated results showed that the benefits of surgery become more pronounced over time. Between 10 and 18 years after treatment, the number needed to

Table 2. Randomized Clinical Trials Comparing Surgery, Radiation Therapy, and Expectant Management Approaches for Patients With Localized Prostate Cancer

	Prostate Cancer Intervention versus Observation Trial (PIVOT)	Scandinavian Prostate Cancer Group (SPCG) Study 4	Prostate Testing for Cancer and Treatment (ProtecT)
Source	Wilt et al,[31] 2012	Bill-Axelson et al,[32] 2014	Hamdy et al,[41] 2016 Donovan et al,[42] 2016
No. of participants	731	695	1643
Median follow-up, y	10	13.4	10
Cohort			
Age, y	≤75	<75	50-69
PSA level, ng/mL	<50	<50	<20
Bone scan	Negative	Negative	Negative (performed if PSA level ≥10 ng/mL or Gleason score ≥3 + 4)
Life expectancy, y	≥10	≥10	≥10
Localized prostate cancer diagnosis year range	1994-2002	1989-1999	1999-2009
Summary	70% Had Gleason score ≤3 + 3 55% Had clinical stage ≤T1c 66% Had PSA level ≤10 ng/mL	61% Had Gleason score ≤3 + 3 24% Had clinical stage ≤T1c 52% Had PSA level ≤10 ng/mL	77% Had Gleason score 3 + 3 76% Had clinical stage of T1c 90% Had PSA level ≤10 ng/mL
No. of sites	44 Veterans Affairs Health System; 8 NCI	14	337 primary care centers
Location	United States	Sweden, Finland, Iceland	9 UK cities
Comparison groups	Surgery vs watchful waiting	Surgery vs watchful waiting	Surgery vs radiation therapy vs active monitoring
Mortality, %			
All cause	47.0 vs 49.9 (P = .22)[a]	57.6 vs 71.0 (P < .001)[a,b]	9.9 vs 10.1 vs 10.8 (P = .87)[b]
Prostate cancer	5.8 vs 8.4 (P = .09)	18.2 vs 28.4 (P = .001)[b]	0.9 vs 0.7 vs 1.5 (P = .48)[a,b]
Outcomes, %			
Metastasis	Bone: 4.7 vs 10.6 (P < .001)	Distant: 25.6 vs 39.7 (P < .001)[b]	2.4 vs 2.9 vs 6.1 (P = .004)[b]
Urinary incontinence at 2 y	17.1 vs 6.3 (P < .001)[c]		≥1 Urine pad/d: 20.1 vs 4.1 vs 3.8 (P < .001)
Erectile dysfunction (insufficient firmness) at 2 y	81.1 vs 44.1 (P < .001)		81.1 vs 66.0 vs 52.9 (P < .001)
Bowel dysfunction (≥moderate problem) at 2 y	12.2 vs 11.3 (P = .74)		1.5 vs 6.3 vs 2.5 (P = .003)
Other		Hormonal therapy: 41.8 vs 67.5 (P < .001)[b]	Clinical progression: 8.3 vs 8.4 vs 20.6 (P < .001)[b]
Prostate cancer characteristics	Poor accrual (initially designed for 2000 men); unhealthy study cohort (5-fold greater mortality than ProtecT); surgery reduced mortality in subgroups (eg, PSA level >10 ng/mL); bilateral nerve sparing in 61 of 364 in surgery group	Mostly unscreened men with palpable tumor (76% clinical stage ≥T2) and high PSA level (>10 ng/mL for 47% of cohort); long follow-up (up to 23.2 y); benefit of surgery most notable in men aged <65 y and in those with intermediate risk disease (eg, Gleason score of 7 and PSA level of 10-20 ng/mL)	Excluded most men with high-risk disease (eg, PSA level ≥20 ng/mL); trial preceded key advances in surgery and radiation; active monitoring did not require repeat biopsy and included men with Gleason score 3 + 4 or with worse disease; lower than expected event rate (1% observed vs 10%-15% estimated for prostate cancer mortality); bilateral nerve sparing in 205 of 553 in surgery group

Abbreviations: NCI, National Cancer Institute; PSA, prostate-specific antigen.

[a] Primary end point.

[b] Outcomes converted from incidence to absolute risk.

[c] Defined as "have a lot of problems with urinary dribbling," "lose larger amounts of urine than dribbling but not all day," "have no control over urine," or "have an indwelling catheter."

treat to avoid 1 death with radical prostatectomy declined from 20 to 8 men.[32] This time interval also saw significant reductions in metastatic disease and need for androgen deprivation therapy (ADT).[32] In the ProtecT trial, both surgery and radiation compared with active monitoring reduced the risk of clinical progression (8.3% vs 8.4% vs 20.6%, respectively; P < .001) and metastatic disease (2.4% vs 2.9% vs 6.1%; P = .004), which could translate into mortality differences with longer follow-up. Table 2 provides further details from these trials.

ProtecT also provides the first randomized comparison of surgery and radiation. Previously, a meta-analysis of mostly observational studies suggested lower overall and prostate cancer mortality with surgery.[44] However, no difference was found in prostate cancer mortality, overall mortality, or metastases in ProtecT. This trial reported significant differences in functional outcomes such as men treated with radiation had better urinary control and sexual function but more nocturia and bowel dysfunction compared with men who underwent surgery.[41,42]

Two prospective, population-based cohort studies conducted in the United States provide additional information regarding the adverse effects of treatment.[45,46] These studies revealed short-term decrements in urinary obstruction and irritation, bowel, and hormonal function after radiation and long-term declines in sexual function and urinary control after surgery relative to men on active

surveillance. In contrast, some men experienced measurable improvements in urinary obstruction and irritation after radical prostatectomy, particularly those with baseline deficits.[45,46] These findings provide important information encouraging shared decision making in prostate cancer treatment.

One challenge in interpreting data from randomized clinical trials has been the concurrent evolution of surgery and radiation. In surgery, open radical prostatectomy has been largely replaced with robotic radical prostatectomy. Two meta-analyses of observational studies suggest that robotic surgery is associated with better 1-year urinary and sexual function outcomes compared with open surgery.[47,48] However, in a single-center randomized clinical trial involving 326 men, robotic prostatectomy resulted in less blood loss and a shorter hospitalization compared with open prostatectomy but with no significant difference in positive margin rate or 3-month functional outcomes.[49] Although randomized, this study included 2 very high volume surgeons and therefore may not be generalizable.

Radiation therapy also has undergone technological advances. Similar to surgery, intensity-modulated radiation therapy has mostly replaced 3D-conformal radiation. Both approaches use computerized software and cross-sectional imaging for planning; however, intensity-modulated radiation therapy delivers nonuniform radiation beams that can conform to irregularly shaped organs, thus reducing radiation to surrounding tissues and subsequent urinary and bowel toxicity.[50,51] As a result, higher doses of radiation can be delivered to the prostate (ie, dose escalation), resulting in improved cancer control.[52-54] Hypofractionation shortens the duration of treatment by delivering radiation in higher doses but in fewer sessions. Even though hypofractionation offers comparable cancer efficacy outcomes vs traditional radiation,[55,56] some trial data report a modest increase in acute bowel and late urinary toxicity.[57,58]

Stereotactic body radiation therapy is an extreme form of hypofractionation that delivers external beam radiation in 5 to 7 sessions using specialized, image-guided planning and monitoring. Phase 2 studies indicate comparable short-term cancer control but potentially greater urinary toxicity.[59] Certain centers report favorable results with high dose–rate brachytherapy.[60] In contrast to low dose–rate brachytherapy (ie, permanent radioactive seeds), this method delivers high-dose radiation via temporary catheters over several sessions. A randomized clinical trial assessing the addition of high dose–rate brachytherapy to external beam radiation in 218 men demonstrated improved local control albeit at dosages lower than contemporary standards.[61] Across these modalities, technical advancements persist relating to positioning, localization, and tracking.

With advances in imaging and intent to reduce treatment-related morbidity, focal treatment of tumors with cryotherapy, high-intensity-focused ultrasound, laser ablation, brachytherapy, or other forms of energy also have been pursued. Existing cohort studies tend to include men with less-aggressive cancer but demonstrate variable treatment success rates with residual tumor reported in 5.1% to 45.9% of cases (0%-13.4% with significant disease).[62] Randomized clinical trials comparing focal therapy with active surveillance, prostatectomy, or radiation are needed to establish the utility of focal therapy in the treatment of prostate cancer.

For certain men, combination therapy may be indicated.[7,29] Clinical guidelines recommend the concurrent administration of ADT in men receiving radiation, particularly those with significant disease.[7] Even with advances in radiation such as dose escalation, randomized clinical trials have confirmed the oncological benefits (eg, local control, disease progression, survival) of short-term (6 months) ADT for intermediate-risk disease and long-term (≥24 months) ADT for high-risk disease.[63,64] For men treated with surgery, randomized clinical trials support the benefits of adjuvant radiation on local control and biochemical recurrence for those with adverse pathology (eg, T3 disease, positive margins).[65,66] As a result, adjuvant radiation should be discussed with patients both before and after surgery.[29] Most recently, a randomized clinical trial of 760 men studied the effect of ADT and radiation therapy for men with biochemical recurrence after surgery.[67] At 12 years, concurrent ADT and radiation significantly reduced metastasis and mortality compared with radiation therapy alone.

Treatment for Metastatic Prostate Cancer

Androgen deprivation therapy continues to be the first-line treatment for men with metastatic prostate cancer. However, this therapy has been associated with toxicity. In addition to established adverse effects (eg, decreased bone mineral density, metabolic changes, sexual dysfunction, hot flashes), cardiac morbidity and cognitive dysfunction have been reported.[68,69] A meta-analysis found no link between ADT and increased cardiovascular death,[70] whereas a post hoc analysis of clinical trial data suggests that cardiac morbidity may exist for patients with preexisting health problems.[71] In view of these concerns, intermittent ADT has been investigated. A meta-analysis reported an association of intermittent ADT with noninferiority compared with continuous ADT with respect to disease progression, cancer-specific survival, and overall survival.[72] Although many men do not achieve objective testosterone recovery during therapy breaks, some report gains in physical or sexual function.[72]

Two randomized clinical trials have highlighted an emerging role for docetaxel, which was previously reserved for patients who did not respond to ADT. In the ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED),[73] 790 men with metastatic disease were randomized to ADT with or without docetaxel. Docetaxel increased median survival from 44.0 to 57.6 months (HR, 0.61; 95% CI, 0.47-0.80) and delayed progression from 11.7 to 20.2 months (HR, 0.61; 95% CI, 0.51-0.72) with greater benefit in men with high-volume disease (ie, visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis).[73] In the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE)[74] trial, there were 2962 men with locally advanced or metastatic prostate cancer. Docetaxel extended the time to biochemical recurrence, progression, or death from prostate cancer by 17 months (HR, 0.61; 95% CI, 0.53-0.70) and overall survival by 10 months (HR, 0.78; 95% CI, 0.66-0.93).[74] In both studies, docetaxel was well tolerated with 86% (CHAARTED) and 77% (STAMPEDE) of participants in the intervention group completing the intended cycles.[73,74]

In many cases, metastatic prostate cancer is or becomes unresponsive to ADT (ie, metastatic castration–recurrent prostate cancer). Since 2010, multiple drugs and treatment innovations have been shown to improve survival and quality of life in randomized clinical trials (**Table 3** and **Table 4**).[75-82] Two of these drugs act on

Table 3. New Drugs for Metastatic Prostate Cancer Based on Randomized Clinical Trials

	Drug Name					
	Abiraterone Acetate[75,76]	Cabazitaxel[77]	Denosumab[78]	Enzalutamide[79,80]	^{223}Radium Dichloride[81]	Sipuleucel-T[82]
Mechanism of action	Selective inhibitor of androgen synthesis	Tubulin-binding taxane	Monoclonal antibody against receptor activator of nuclear factor κ-B ligand, inhibits osteoclast formation or propagation	Targeted androgen receptor signaling inhibitor	α-Emitter particle that selectively binds areas of high bone turnover	Autologous cellular immunotherapy
Prostate cancer progression	Castration recurrent	Castration recurrent (after treatment with docetaxel)	Castration recurrent with bony metastases	Castration recurrent	Castration recurrent with bony metastases	Castration recurrent without or with minimal symptoms
Control group	Placebo	Mitoxantrone	Zoledronic acid	Placebo	Placebo	Placebo
No. of participants		755	1904		921	512
Without previous docetaxel treatment	1088[76]			1717[80]		
After docetaxel treatment	1195[75]			1199[79]		
Primary outcomes, HR (95% CI)	Without previous docetaxel treatment[76]: overall survival, 0.75 (0.61 to 0.93); radiographic progression-free survival, 0.53 (0.45 to 0.62) After docetaxel treatment[75]: overall survival, 0.65 (0.54 to 0.77)	Overall survival, 0.70 (0.59 to 0.83)	Skeletal-related events, 0.82 (0.71 to 0.95)	Without previous docetaxel treatment[80]: overall survival, 0.71 (0.60 to 0.84); radiographic progression-free survival, 0.19 (0.15 to 0.23) After docetaxel treatment[79]: overall survival, 0.63 (0.53 to 0.75)	Overall survival, 0.70 (0.58 to 0.83)	Overall survival, 0.78 (0.61 to 0.98)
Secondary outcomes, HR (95% CI)	Without previous docetaxel treatment[76]: PSA progression-free survival, 0.49 (0.42 to 0.57); opiate use, 0.69 (0.57 to 0.83); chemotherapy, 0.58 (0.49 to 0.69) After docetaxel treatment[75]: PSA progression-free survival, 0.58 (0.46 to 0.73); radiographic progression-free survival, 0.67 (0.58 to 0.78)	Progression-free survival, 0.74 (0.64 to 0.86); PSA progression-free survival, 0.75 (0.63 to 0.90); radiographic progression-free survival, 0.61 (0.49 to 0.76); pain progression-free survival, 0.91 (0.69 to 1.19)	Overall survival, 1.03 (0.91 to 1.17); progression-free survival, 1.06 (0.95 to 1.18)	Without previous docetaxel treatment[80]: PSA progression-free survival, 0.17 (0.15 to 0.20); skeletal-related events, 0.72 (0.61 to 0.84); chemotherapy, 0.35 (0.30 to 0.40); decline in quality of life, 0.63 (0.54 to 0.72) After docetaxel treatment[79]: PSA progression-free survival, 0.25 (0.20 to 0.30); radiographic progression-free survival, 0.40 (0.35 to 0.47); skeletal-related events, 0.69 (0.57 to 0.84)	Skeletal-related events, 0.66 (0.52 to 0.83); PSA progression-free survival, 0.64 (0.54 to 0.77); increase in quality of life, 25% vs 16% (P = .02); change in quality of life score, −2.7 vs −6.8 (P = .006)	Prostate cancer mortality, 0.77 (0.61 to 0.98); radiographic progression-free survival, 0.95 (0.77 to 1.17)
Notable adverse events	Hypokalemia, hypertension, edema	Neutropenia, diarrhea	Hypocalcemia, rare osteonecrosis	Hypertension, hot flashes, falls, seizures	Hematologic (eg, low platelet count), edema	Flu-like symptoms
Comments	Administered with prednisone	Only 28% completed all 10 cycles; administered with prednisone	Recommend concurrent calcium and vitamin D supplementation	Complete disappearance of radiographic measurable disease in 20% of patients		No objective measure of response (eg, PSA level); requires leukapheresis

Abbreviations: HR, hazard ratio; PSA, prostate-specific antigen.

Table 4. Innovations in Prostate Cancer Care

Type of Innovation	Description	Comment
Diagnosis		
Revised histological grading system	Grades prostate cancer on a scale from 1 to 5 with better discriminatory power than previous system	Unclear how this affects existing risk stratification schema
Magnetic resonance imaging of prostate and prostate biopsy	Multiparametric magnetic resonance imaging offers 89% sensitivity and 73% specificity for detecting prostate cancer; can be used to enhance accuracy of prostate biopsy	Recommended for men with previous negative biopsy
Prognostic biomarkers	Serum-, tissue-, and image-based biomarkers offer prognostic information for cancer behavior	Unclear effect on treatment selection and outcome
Functional imaging with positron emission tomography	Improves detection of local recurrence, regional lymph node metastases, and distant metastases	Limited availability and approval of radiotracers
Treatment		
Shared decision making	Collaborative approach to decision making that combines clinician input with patient preferences and values	Current decision aids have equivocal effect on treatment choice and satisfaction
Active surveillance	Serial monitoring of prostate cancer with the intent to cure; progression carries low risk for 5- to 10-year mortality (<2%) in men with lower-risk disease	Awaiting longer-term follow-up; optimal surveillance strategy to be determined
Technical advances in surgery and radiation therapy	Robotic prostatectomy and dose-escalated or hypofractionated radiation therapy have become commonplace; focal treatment now being studied	Questions on quality assurance and comparative effectiveness remain
Combination therapy for localized prostate cancer	Radiation therapy following prostatectomy reduces progression; concurrent androgen deprivation therapy with primary radiation therapy lowers recurrence and improves survival	Accumulation of morbidity may be a consideration
Docetaxel for metastatic prostate cancer responsive to androgen deprivation therapy	Docetaxel is well tolerated and improves survival by 10 to 13 months compared with standard androgen deprivation therapy	May be most beneficial for men with high-volume metastatic disease
Management of metastatic prostate cancer unresponsive to androgen deprivation therapy	Cancer vaccine, advanced hormonal therapies, and bone-targeting agents significantly improve survival and quality of life in some cases	Emerging research on combination types, sequencing, and personalized selection
Prostate cancer survivorship	Survivorship care plans that encompass health promotion, cancer surveillance, and symptom management now endorsed	Operationalization and implementation remain as barriers

the androgen axis: abiraterone acetate inhibits androgen biosynthesis, whereas enzalutamide interferes with androgen-receptor signaling (Table 3). Whether before or after treatment with docetaxel, these therapies slowed disease progression and improved survival and secondary end points (eg, skeletal-related events, pain, quality of life).[75,76,79,80] Sipuleucel-T, an autologous cellular immunotherapy, became the first FDA-approved cancer vaccine in the United States, increasing median survival by 4.1 months compared with placebo. This therapy is typically reserved for men who are asymptomatic or minimally symptomatic and may offer a greater effect when administered to patients when they have low PSA levels.[82,83] Cabazitaxel, a novel tubulin-binding taxane, also increased median survival by 2.4 months compared with mitoxantrone. However, many trial participants did not complete treatment due to high toxicity (eg, neutropenia, diarrhea).[77]

Bone health has been an additional therapeutic focus in the treatment of metastatic prostate cancer unresponsive to ADT. Denosumab, a human monoclonal antibody acting against the receptor activator of nuclear factor κ-B ligand, promotes osteoclast formation and propagation. Compared with zoledronic acid, the established preventive therapy for men with castration-recurrent prostate cancer and bony metastases, denosumab delayed the first skeletal-related event by 3.6 months with similarly high toxicity levels but greater ease of administration.[80] ^{223}Radium, an α-emitter particle that selectively binds and targets bony metastases, prolonged median overall survival by 3.6 months and time to first skeletal-related event by 5.8 months compared with placebo and maintained these benefits irrespective of concurrent bisphosphonate use (eg, zoledronic acid). ^{223}Radium also slowed the decline in quality of life with some men exhibiting an overall improvement.[81]

Multimodal therapy and precision medicine may emerge as future advances in the care of metastatic prostate cancer. Recent data suggest that men with regional lymph node involvement may benefit from radiation therapy in addition to ADT.[84,85] Moreover, a randomized clinical trial evaluating ADT plus docetaxel and estramustine vs ADT alone prior to local therapy (87% radiation, 6% prostatectomy) for men with high-risk prostate cancer found a 29% reduction in disease relapse or progression for men receiving ADT plus docetaxel and estramustine.[86] Accordingly, local therapy may be appropriate for lymph node–positive disease and potentially for men with a limited number of metastases. Simultaneously, treatment of metastatic prostate cancer can be increasingly tailored to an individual's tumor molecular biology. Based on recent studies, DNA repair gene aberrations (eg, *BRCA1*, *BRCA2*) or androgen receptor variants can be used to select more effective treatments (eg, docetaxel vs enzalutamide or abiraterone acetate).[87,88]

Prostate Cancer Survivorship

With 5-year cancer survival rates approaching 100%,[2,31-33,41,89] virtually all men diagnosed with prostate cancer will face the sequelae of their diagnosis and treatment. To help patients, caregivers, and clinicians navigate this aspect of care, the American Cancer Society has developed guidelines for prostate survivorship (ie, the life and health of men following treatment).[89] These guidelines recommend detailed survivorship plans that encompass health promotion, cancer surveillance, and screening as well as information regarding physical and psychosocial burdens, social support, and care coordination.

In this context, pharmacological, psychological, and behavioral supports have been developed to reduce distress that may

manifest during survivorship. For affected men, phosphodiesterase type 5 inhibitors can improve sexual function and couples or group therapy can help improve sexual experience.[90-93] Pelvic floor training can help restore urinary control for men with incontinence after prostatectomy.[94,95] Diet and exercise interventions have demonstrated benefit in quality of life, especially for those taking ADT for metastatic disease.[96,97] Behavioral therapy (whether in person or online) can help men cope with the distress of cancer- and treatment-related adverse effects.[98,99] Through such supportive interventions, cancer survivors can thrive through the chronicity of surveillance and persevere through long-term adverse effects.

Conclusions

Advances in the diagnosis and treatment of prostate cancer have improved the ability to stratify patients by risk and allowed clinicians to recommend therapy based on cancer prognosis and patient preference. Initial treatment with chemotherapy can improve survival compared with androgen deprivation therapy. Abiraterone, enzalutamide, and other agents can improve outcomes in men with metastatic prostate cancer resistant to traditional hormonal therapy.

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