

Management of Early-Stage Prostate Cancer

Neal Shore, MD

Abstract

Prostate cancer is the second-most common cancer diagnosed in men, with a median age of diagnosis of 66 years. Early disease is often asymptomatic, and diagnosis is based on abnormal prostate specific antigen (PSA) levels followed by a transrectal ultrasound-guided biopsy, digital rectal exam, or both. Disease staging after diagnosis is used to evaluate prognosis and determine the treatment approach. Biomarkers are useful for prostate cancer screening and as prognostic factors. The most important biomarker is PSA; however, newer prognostic factors may be more specific for prostate cancer. The goal of treatment is to identify patients who are most likely to benefit from therapy while minimizing treatment-related complications. Treatment options include watchful waiting/active surveillance, radical prostatectomy, external beam radiation therapy, brachytherapy, cryotherapy, androgen deprivation therapy, and combination therapy. Additional studies to evaluate comparative effectiveness and cost-effectiveness of therapies would be beneficial, as availability of these data are limited.

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For author information and disclosures, see end of text.

As the second most common cancer diagnosed in men, prostate cancer represents a considerable health, economic, and social burden in the United States and worldwide.¹ Treatments for prostate cancer have the potential to improve outcomes by prolonging survival and reducing symptoms. Such treatments can be associated with significant costs, causing payers to closely scrutinize clinical and economic data before approving reimbursement.

In 2009, the Institute of Medicine identified the treatment of localized prostate cancer as a top priority for comparative effectiveness research.² This article will provide a summary of management strategies for localized prostate cancer and will review the results of cost-effectiveness research in treatments for early-stage prostate cancer. The impact on costs, survival, and patient-reported outcomes (PROs) of those treatments will be discussed.

With a median age at diagnosis of 66 years, prostate cancer predominantly affects older men.³ The onset of prostate cancer is asymptomatic in most cases. However, increased urinary frequency, weak urinary stream, urinary obstruction, lower urinary tract infections, and inadequate bladder emptying may be found. Other symptoms may only occasionally include erectile dysfunction and hematuria.

Diagnosis

The diagnosis of prostate cancer is established by transrectal ultrasound-guided biopsy, typically after abnormal serum prostate specific antigen (PSA) level changes, digital rectal examination (DRE), or both. Classification of histopathologic specimens can vary widely due to subjective assessments by pathologists. Interobserver variation in histopathological assessment can have major clinical consequences affecting disease staging, monitoring, and treatment recommendations.⁴ Screening methods for prostate cancer using serum PSA or DRE can also be problematic. Interpretation of serum PSA may be influenced by analytical factors (eg, pre-analytical sample

handling, laboratory processing, assay performance, test standardization) or biological variation (eg, medication, physical and sexual activity, prostate size).⁵ DRE has been recognized to be extremely subjective with high interobserver variability, making it a nonreliable tool to detect prostate cancer.^{6,7}

Disease Staging

Prostate cancer diagnosis involves staging of the cancer tissue in order to aid prognosis and inform treatment choice. Cancer stage is determined using a number of systems, of which the most widely used is the tumor-nodes-metastasis (TNM) staging system.⁸ In TNM staging, information about the tumor (T), nearby lymph nodes (N), and distant organ metastases (M) is combined and a stage is assigned to specific TNM groupings. The combination of T, N, and M categories determines the stage of the disease.

TNM describes the progressive stages of cancer depending on its size and location:

- T stage describes local cancer confined to the prostate.
- N stage describes the spread of metastases to the nearest lymph nodes through the lymphatic system.
- M stage describes the spread of metastases to distant sites through the lymph or blood system. In prostate cancer, metastases frequently occur in lymph nodes and bones.

Prostate cancer is also evaluated based on the anatomy or histology of the cancerous cells according to the Gleason grade. If cancers are made up of a mixture of cell types, they are evaluated according to the Gleason score, which takes into consideration the Gleason grade of the 2 most prevalent cell types. To obtain a patient's Gleason score, the Gleason grade of these 2 most prevalent cell types are added together. The Gleason score can range from 2 to 10.⁹

A number of biomarkers have been identified in prostate cancer. The most important of these is PSA serum level, which is a useful tool for both prostate cancer screening and assessment of disease progression. A patient's PSA level at the time of diagnosis is often used as an indicator of cancer stage and is a prognostic factor, with higher PSA levels suggesting a more aggressive disease.^{9,10} Additionally, it has also been shown that the rate of PSA level increase (velocity) is predictive of

outcomes such as rate of tumor recurrence after radical prostatectomy.¹¹ Patients whose PSA levels increase by more than 2.0 ng/mL per year before undergoing surgery or radiation therapy may have a higher rate of prostate cancer recurrence.¹²

The proPSA is a molecular form of free PSA (fPSA) that is more likely to be associated with prostate cancer. The Prostate Health Index (PHI), approved in 2012, is a mathematical formula of 3 biomarkers (p2PSA, fPSA, and total PSA) that better distinguishes prostate cancer from benign prostatic conditions in men older than 50 years with a total serum PSA between 4 and 10 ng/mL and in whom the DRE is normal.¹³ Another test, the 4K score, has recently become available. This adds one more PSA isoform to the 3 used in the PHI (kallikrein-related peptide 2) to generate a score that is used to distinguish between pathologically insignificant and aggressive disease and to prevent unnecessary biopsies.¹³ A third test, ProMark, is a new biopsy-based prostate cancer prognostic test that detects multiple protein biomarkers using an automated immunofluorescent imaging platform. It has been shown to be highly predictive in aggressive forms of prostate cancer.¹³

The extent of prostate cancer is classified into stages I through IV, which are determined by TNM categories and are combined with the Gleason histologic score and serum PSA level.⁹ Stage I and II tumors are confined to the prostate; stage III tumors are more locally advanced; and stage IV tumors are either locally advanced and invading local adjacent structures or have associated distant metastases.¹⁴ The criteria for stages I to III (early stage) are provided in [Table 1](#).¹⁵

The use of new prognostic factors remains investigational and may help to avoid unnecessary treatment and identify patients with poor outcomes who would be candidates for trials of adjuvant treatment.¹⁶ PCA-3 test is a urine-based marker measured from urine collected after a DRE and prostatic massage. Highly specific for prostate cancer and not affected by prostate volume and chronic prostatitis, PCA-3 is also considered to be helpful in decision making with regard to potential rebiopsy and in the follow-up of patients under active surveillance.¹⁷ ConfirmMDx is a tissue-based epigenetic assay to improve patient stratification on the decision for repeat biopsy. It is performed on the archived tissues from the previous negative biopsy and detects an epigenetic field effect resulting from increased hypermethylation of prostate cancer specific genes. This field effect around

■ Table 1. Anatomic Stage/Prognostic Groups¹⁵

Group	T	N	M	PSA	Gleason
I	T1a–c	N0	M0	PSA <10	Gleason ≤6
	T2a	N0	M0	PSA <10	Gleason ≤6
	T1–2a	N0	M0	PSA X	Gleason X
IIA	T1a–c	N0	M0	PSA <20	Gleason 7
	T1a–c	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA <20	Gleason 7
	T2b	N0	M0	PSA <20	Gleason ≤7
IIB	T2b	N0	M0	PSA X	Gleason X
	T2c	N0	M0	Any PSA	Any Gleason
III	T1–2	N0	M0	PSA ≥20	Any Gleason
	T1–2	N0	M0	Any PSA	Gleason ≥8
IV	T3a–b	N0	M0	Any PSA	Any Gleason
	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

G indicates grade; M, metastasis; N, node; PSA, prostate-specific antigen; T, tumor.
^aWhen either PSA or Gleason is not available, grouping should be determined by T stage and/or either PSA or Gleason as available.
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the cancer lesion can be detected despite the normal histologic appearance of the cells, effectively extending the coverage of the biopsy. This test may help in the identification of high-risk men who require repeat biopsies and men without prostate cancer who may avoid unnecessary repeat biopsies.^{18,19} The assay currently has preliminary reimbursement approval from the MoIDx program, pending an ongoing prospective clinical utility trial.

Promising techniques such as multiparametric magnetic resonance imaging (MRI) are also emerging for detecting, characterizing, and staging the extent of disease. This information can help with diagnosis and with determining treatment strategies for prostate cancer. Results of a recent meta-analysis by de Rooij and colleagues showed a specificity of 0.88 (95% CI, 0.82-0.92) and sensitivity of 0.74 (95% CI, 0.66-0.81) for prostate cancer detection, with negative predictive values (NPVs) ranging from 0.65 to 0.94. No significant differences were found between the subgroups.²⁰

Prostate cancer is more prevalent in old age and may remain asymptomatic for many years; many men die with prostate cancer, but not as a direct result of it. Prostate cancer can be very slow growing and is usually asymptomatic in the early (localized) stages of the disease.

Active treatment may, therefore, be unnecessarily disruptive and harmful for patients whose tumors will never progress to an advanced stage or who are unlikely to live long enough for prostate cancer to become symptomatic. Therefore, strategies such as watchful waiting or active surveillance, which involve delaying treatment until patients experience either evidence of progression or symptoms of a progressive disease, are viable options for some patients with prostate cancer.¹⁴

Currently Available Treatment Options

As therapies for localized prostate cancer continue to evolve, several unifying concepts for all validated treatment approaches have emerged. Prostate cancer treatments have been developed to eradicate the cancer while minimizing treatment-associated side effects and costs. The primary treatment goal for localized prostate cancer is to target patients who are most likely to benefit from intervention and to prevent disability and death while minimizing intervention-related complications.

Individualized treatment for prostate cancer is based on patient-related factors (eg, comorbidities, age, life expectancy, preferences for treatment), disease-related factors (ie, tumor staging, presence of metastatic disease, disease prognosis), and treatment-related factors (eg, likelihood of cure [efficacy/survival rates, reduction in relative risk of death], adverse effects, and potential treatment complications).^{9,21} Although life expectancy is an important consideration in treatment selection, there is no standardization among clinicians for determining life expectancy. Despite their inclusion in practice guidelines,²² actuarial estimates of life expectancy are often underutilized in clinical practice. Patient preferences also vary widely, depending on issues such as perceptions of treatment efficacy related to cancer eradication/control; treatment-related side effects and their impact on health-related quality of life (QOL); treatment costs; personal value systems; influence of spouses and family members; and racial, cultural, and socioeconomic factors.²³

Many different treatment options endorsed in clinical practice guidelines are considered clinically appropriate for early-stage prostate cancer (Table 2).²⁴ For example, intensity-modulated radiation therapy (IMRT), brachytherapy, cryotherapy, and radical prostatectomy are all among the treatments considered appropriate for men with low-risk prostate cancer. Combination therapies, such as brachytherapy combined with radiation therapy, may also be given.²⁴ Even though such treatments are often considered equally appropriate, the risks and

side effects vary for each treatment.

Watchful Waiting/Active Surveillance

Watchful waiting aims to avoid interventional treatment, such as surgery and radiation therapy, in patients who are unlikely to experience significant cancer progression during their remaining lifetime, and thus waits for them to present with advanced symptomatology.²⁵ Another approach to observational management, active surveillance, involves enhanced monitoring of patients (typically with serial PSA, DRE, and rebiopsy) to retain the goal of curative treatment should disease progression occur.²² While observational management avoids treatment-related adverse events, factors that can influence the success of an active surveillance program include the potential for biopsy sampling errors; costs and morbidities from repeat biopsies, compliance with repeat biopsy protocols, and potential physician and patient anxiety that can occur as a result of withholding an interventional treatment.²⁶

Commercially available genomic assays can help inform decision making for patients with newly diagnosed prostate cancer. The Oncotype DX Prostate Cancer Assay tests small tissue samples obtained by needle biopsy for the expression of 12 cancer-related genes representing 4 different biologic pathways. These are combined to calculate the Genomic Prostate Score, which improves risk discrimination for prostate cancer and assists clinicians in selecting appropriate patients for active surveillance.¹³ The Prolaris Score, directly measures tumor cell growth characteristics to stratify risk of disease progression. A total of 46 different gene expressions are tested. High rates of expression are associated with higher risk for disease progression, indicating that therapy or close monitoring may be necessary.¹³

Xia and colleagues performed a study using a simulation model to project prostate cancer mortality with active surveillance followed by radical prostatectomy versus immediate radical prostatectomy in patients with low-risk prostate cancer. Projections from the model

indicated that 20-year disease mortality would be 2.8% for patients on active surveillance and 1.6% for those who received immediate radical prostatectomy. Estimates for lifetime disease mortality were 3.4% for active surveillance and 2.0% for immediate radical prostatectomy. Immediate radical prostatectomy was associated with an average projected increase in life expectancy of 1.8 months. This modest increase in disease-specific survival was offset by the potential benefits of remaining treatment-free an average of 6.4 years on active surveillance versus immediate radical prostatectomy, thus avoiding adverse treatment-related effects and potentially preserving QOL.²⁷

Radical Prostatectomy

Radical prostatectomy is the complete surgical removal of the prostate gland with seminal vesicles, ampulla of vas, and sometimes pelvic lymph nodes. It involves conventional techniques, such as open retropubic or open perineal, and newer techniques, such as laparoscopic and robotic-assisted approaches.¹⁴ The advantages of newer laparoscopic and robotic-assisted approaches include reduced blood loss, faster convalescence, and shorter hospital stays.²⁸

In the Prostate Cancer Intervention Versus Observation Trial (PIVOT), Wilt and colleagues investigated the effectiveness of radical prostatectomy versus watchful waiting in patients with localized prostate cancer. Results of the trial showed no benefit from radical prostatectomy over watchful waiting in the treatment of low-risk prostate cancer in terms of all-cause mortality (hazard ratio [HR], 1.15; 95% CI, 0.80-1.66) or prostate cancer-specific mortality

Table 2. Standard Treatment Options by Stage²⁴

Stage	Standard treatment options
Stage I prostate cancer	Watchful waiting or active surveillance
	Radical prostatectomy
	EBRT, including IMRT
	Brachytherapy
Stage II prostate cancer	Watchful waiting or active surveillance
	Radical prostatectomy
	EBRT, including IMRT
	Brachytherapy
Stage III prostate cancer	EBRT, including IMRT, with or without hormonal therapy
	Hormonal manipulations (orchiectomy or luteinizing hormone-releasing hormone agonist)
	Radical prostatectomy with or without EBRT, including IMRT
	Watchful waiting or active surveillance

EBRT indicates external-beam radiation therapy; IMRT, intensity-modulated radiation therapy.

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at 12 years (HR, 1.48; 95% CI, 0.42-5.24). Compared with watchful waiting, radical prostatectomy was associated with a significant increase in urinary incontinence ($P < .001$) and erectile dysfunction ($P < .001$).²⁹

EBRT

External-beam radiation therapy (EBRT) uses multiple doses of radiation from an external source applied over several days to weeks to eradicate prostate cancer cells and includes conventional radiation therapy, intensity-modulated radiation therapy (IMRT), and other approaches.¹⁴ IMRT allows radiation to be delivered locally to the tumor while minimizing damage to normal tissue, generally resulting in manageable adverse effects.³⁰ In locally advanced as well as high-risk patients, radiation may be combined with hormonal therapy in order to improve efficacy.²²

Sooriakumaran and colleagues conducted an observational study using Swedish registry data to compare the survival outcomes of patients treated with surgery or with radiation therapy for prostate cancer. For patients with non-metastatic prostate cancer, surgery was favored over radiation therapy in terms of prostate cancer mortality (adjusted HR, 1.76 for radiation therapy vs surgery; 95% CI, 1.49-2.08).³¹ The observational study did not include a safety analysis. However, the treatment-related adverse events have been previously reported for both approaches. Well-known risks commonly associated with radiation therapy treatment are for gastrointestinal and genitourinary toxicities.³²

Brachytherapy

Brachytherapy uses radioactive implants placed under radiologic guidance to emit radiation to cells affected by cancer.¹⁴ Permanent (low-dose rate, or LDR) or temporary (high-dose rate, or HDR) brachytherapy may be used. This therapy may also be used in combination with EBRT.

Vargas and colleagues evaluated long-term outcomes in patients with localized prostate cancer who were treated with brachytherapy. Results supported the benefit of brachytherapy across low-, intermediate-, and high-risk groups. The 10-year biochemical control rate was 98% for low-risk patients, 94% for intermediate-risk patients, 88% for high-risk patients who have 1 high-risk factor, and 78% for all high-risk patients ($P < .001$). The disease-specific survival was 99% for low-risk, 98% for intermediate-risk, and 84% for high-risk patients ($P < .001$). There was no significant difference in outcomes between the low-risk and intermediate-risk groups ($P > .3$).³³

Cryotherapy

Cryotherapy is a thermoablative therapy available to patients with localized prostate cancer.⁹ This technique involves the destruction of cells through rapid freezing and thawing, using transrectal guided probe placement and injection of freezing/thawing cryo gases.¹⁴ Donnelly and colleagues conducted a randomized, unblinded, non-inferiority trial to compare cryoablation with EBRT in patients with localized prostate cancer. At 36 months, no difference was observed in the treatment failure rate for cryotherapy and EBRT (23.9% and 23.7%, respectively; difference, 0.2%; 95% CI, -10.8% to 11.3%). Similarly, there was no difference in overall survival between cryoablation and EBRT ($P = .78$).³⁴ Poorer sexual function was reported by patients who received cryoablation compared with those who received EBRT.³⁵

Of note, focal therapy is emerging as a treatment option for clinically localized prostate cancer designed to reduce the morbidities associated with EBRT and radical prostatectomy. However, this therapy is still in its infancy, and researchers are currently evaluating focal therapy and its potential role among other treatment modalities for clinically localized prostate cancer.³⁶

Hormone Therapy: Androgen Deprivation Therapy

Androgen deprivation therapy (ADT) involves injectable medications to lower testosterone levels or surgical removal of testicles to lower or block circulating androgens.¹⁴ The goal of ADT is to reduce the level of testosterone and other androgens to castrate levels, based on the fact that testosterone is a key driver of prostate cancer. Various adverse effects are associated with ADT, including decreased libido, impotence, hot flashes, osteopenia with increased fracture risk, metabolic alterations, and changes in mood and cognition.³⁷

Pagliariulo and colleagues analyzed data from randomized controlled trials and population-based studies to evaluate the role of ADT as monotherapy in patients with nonmetastatic disease or in combination with radiation therapy or after surgery, and in patients with metastatic disease. Findings of the analysis showed no benefit from ADT monotherapy in patients with nonmetastatic disease. ADT in combination with radiation therapy (<72 Gy) delayed progression and prolonged survival in patients with high-risk disease. There was a lack of data on the postoperative use of ADT. Benefits were also shown in patients with metastatic disease in terms of QOL, reduction of disease-related morbidity, and possibly survival.³⁸

Table 3. Comparison of Guideline Recommendations^{22,40-43}

Treatment	NCCN	AUA	ESMO	EAU	NICE
Watchful waiting/ active surveillance	<p>Can be offered to men with:</p> <ul style="list-style-type: none"> • very low risk prostate cancer and life expectancy of ≥ 20 years • low-risk disease and life expectancy of ≥ 10 years • low-risk disease and life expectancy of ≥ 10 years as an alternative to radiation therapy or radical prostatectomy 	<p>Can be offered to men with:</p> <ul style="list-style-type: none"> • low-risk localized prostate cancer • intermediate-risk localized prostate cancer • high-risk or locally advanced prostate cancer 	<p>Can be offered to men with:</p> <ul style="list-style-type: none"> • low-risk localized prostate cancer • intermediate-risk localized prostate cancer • intermediate-risk, high-risk or locally advanced prostate cancer who are not suitable for, or unwilling to have, radical treatment 	<p>Can be offered to men with:</p> <ul style="list-style-type: none"> • early-stage prostate cancer • Active surveillance recommended for men with localized stage T1a prostate cancer and a life expectancy > 10 years, and for asymptomatic patients with stage T1b-T2b cancer 	<p>First option for men with:</p> <ul style="list-style-type: none"> • low-risk localized prostate cancer who are eligible for radical treatment • Can be offered to men instead of immediate radical prostatectomy or radiation therapy • Should not be offered to men with high-risk localized or locally advanced prostate cancer
Radical prostatectomy	<p>Can be offered to men with:</p> <ul style="list-style-type: none"> • low risk of recurrence and life expectancy of ≥ 20 years • intermediate, high, or very high risk of recurrence regardless of life expectancy 	<p>Can be offered to men with:</p> <ul style="list-style-type: none"> • low-risk localized prostate cancer • intermediate-risk localized prostate cancer • high-risk or locally advanced prostate cancer 	<p>Can be offered to men with:</p> <ul style="list-style-type: none"> • low-risk localized prostate cancer • intermediate-risk localized prostate cancer • high-risk or locally advanced prostate cancer 	<p>Can be offered to men with localized disease and a long life expectancy</p>	<p>Can be offered to men with:</p> <ul style="list-style-type: none"> • intermediate-risk localized or locally advanced prostate cancer • high-risk localized or locally advanced prostate cancer when there is a realistic prospect of long-term disease control
EBRT	<p>Can be offered to men with:</p> <ul style="list-style-type: none"> • low risk of recurrence and life expectancy of ≥ 20 years • intermediate risk of recurrence regardless of life expectancy 	<p>Can be offered to men with:</p> <ul style="list-style-type: none"> • low-risk localized prostate cancer • intermediate-risk localized prostate cancer • high-risk or locally advanced prostate cancer 	<p>Can be offered to men with:</p> <ul style="list-style-type: none"> • low-risk localized prostate cancer • intermediate-risk localized prostate cancer 	<p>Can be offered to men with low-risk (dose of ≥ 74 Gy) and intermediate-risk (dose of 78 Gy) prostate cancer</p>	<p>Can be offered to men with:</p> <ul style="list-style-type: none"> • intermediate-risk localized or locally advanced prostate cancer • high-risk localized or locally advanced prostate cancer when there is a realistic prospect of long-term disease control
Brachytherapy	<p>Can be offered as initial or adjuvant therapy to men with: low, intermediate, high, or very high risk of recurrence</p>	<p>Can be offered to men with:</p> <ul style="list-style-type: none"> • low-risk localized prostate cancer • intermediate-risk localized prostate cancer • high-risk or locally advanced prostate cancer 	<p>Can be offered to men with:</p> <ul style="list-style-type: none"> • low-risk localized prostate cancer • intermediate-risk localized prostate cancer 	<p>Low-dose-rate (LDR) brachytherapy can be offered to men with low-risk prostate cancer</p>	<p>No guidance</p>

(Continued)

Table 3. Comparison of Guideline Recommendations^{22,40-43} (Continued)

Treatment	NCCN	AUA	ESMO	EAU	NICE
ADT	Can be offered as adjuvant therapy to men with: <ul style="list-style-type: none"> • low risk of recurrence and lymph node metastasis • Can be offered as initial or adjuvant therapy to men with intermediate, high, or very high risk of recurrence 	Adjuvant ADT recommended for high-risk or locally advanced prostate cancer	ADT alone should not be offered to men with: <ul style="list-style-type: none"> • low-risk localized prostate cancer • intermediate-risk localized prostate cancer • high-risk localized or locally advanced prostate cancer 	Adjuvant ADT recommended for locally advanced prostate cancer	No guidance
Combination therapy	Can be offered as adjuvant therapy to men with: <ul style="list-style-type: none"> • low risk of recurrence and lymph node metastasis • Can be offered as initial or adjuvant therapy to men with intermediate, high, or very high risk of recurrence 	Can be offered to men with high-risk or locally advanced prostate cancer	Can be offered to men with high-risk or locally advanced prostate cancer	Recommended for locally advanced prostate cancer (T3-T4 N0 M0)	No guidance

AUA indicates American Urological Association; EAU, European Association of Urology; ESMO, European Society of Medical Oncology; NCCN, National Comprehensive Care Network; NICE, National Institute of Health and Care Excellence.

Combination Therapies

Combination therapies with ADT and EBRT have shown improved cancer control and overall survival in early-stage prostate cancer for intermediate- and high-risk patients. A phase 3 study by Widmark and colleagues compared ADT with and without EBRT in patients with locally advanced prostate cancer. The study included 875 patients who received endocrine therapy (3 months of combined androgen blockade followed by flutamide monotherapy). Patients were randomized to receive endocrine therapy alone or endocrine therapy plus EBRT. Results of the study demonstrated a beneficial impact of additional EBRT versus endocrine therapy alone in terms of cause-specific (11.9% vs 23.9%; $P < .001$) and overall mortality at 10 years (29.6% vs 39.4%; $P = .004$). The combination group reported slightly more frequent urinary, rectal, and sexual problems after 5 years.³⁹

Recent Guidelines for Stage-Specific Treatment

Several treatment options for localized prostate cancer

are recommended in clinical practice guidelines, including active surveillance, radical prostatectomy, EBRT, brachytherapy, and combination treatments. The major guidelines for prostate cancer are discussed in this section and summarized in [Table 3](#).^{22,40-43}

NCCN

The National Comprehensive Cancer Network (NCCN) panel remains concerned about overdiagnosis and overtreatment of prostate cancer, and recommends that patients and their physicians consider active surveillance based on careful consideration of the patient’s prostate cancer risk profile, age, and health. Active surveillance is considered a reasonable strategy for many patients due to the limited aggressiveness of many localized prostate cancers.

Treatment recommendations are based on predicted life expectancy and level of risk or recurrence. The risk groups defined by the NCCN are based on tumor staging, Gleason score, PSA, and biopsy findings. The NCCN guideline recommends active surveillance for men with

very low-risk prostate cancer and a life expectancy of 20 years or more, or those with low-risk disease and a life expectancy of 10 years or more. Active surveillance is also an option for low-risk patients with a life expectancy of 10 years or more as an alternative to EBRT or radical prostatectomy. EBRT is an acceptable strategy for patients with low risk of recurrence and life expectancy of 20 years or more and also for those with an intermediate risk of recurrence regardless of life expectancy.²²

AUA

The American Urological Association (AUA) has considered the following as viable monotherapy options for clinically localized, low-risk prostate cancer: active surveillance, radical prostatectomy, EBRT, and interstitial brachytherapy. AUA treatment recommendations are classified according to risk strata (based on tumor staging, Gleason score, and PSA). Active surveillance, interstitial prostate brachytherapy, EBRT, and radical prostatectomy are appropriate monotherapy treatment options for patients with low-, intermediate, or high-risk localized prostate cancer. However, recurrence rates are high in patients with high-risk localized prostate cancer, and the use of ADT or combination therapies can improve survival.⁴⁰

ESMO

The European Society of Medical Oncology (ESMO) clinical practice guidelines define risk groups for clinically localized disease by tumor staging, Gleason score, and PSA. Recommended options for low-risk patients include active surveillance, radical prostatectomy, EBRT, brachytherapy with permanent implants or high dose rate brachytherapy with temporary implants. Recommended options for intermediate-risk patients include radical prostatectomy, EBRT, and brachytherapy with permanent implants. Recommended options for high-risk patients include radical prostatectomy or EBRT plus neoadjuvant treatment. The ESMO guideline does not recommend immediate hormone therapy alone for low-, intermediate-, or high-risk (or locally advanced) groups. Watchful waiting with delayed hormone therapy is an option, in the event of symptomatic progression, for patients who are not appropriate for or are unwilling to receive radical treatment.⁴¹

EAU

Localized prostate cancer is classified by the European Association of Urology (EAU) into 3 risk categories according to tumor staging, Gleason score, and PSA.⁴²

For patients with early-stage prostate cancer, there are 2 options for the conservative management of cancer: watchful waiting and active surveillance. Active surveillance is recommended for patients with localized stage T1a prostate cancer and a life expectancy of greater than 10 years, and for asymptomatic patients with stage T1b-T2b cancer. Monitoring for disease progression with PSA, transrectal ultrasound (TRUS), and rebiopsy is recommended.⁴²

For patients with localized disease and a long life expectancy, active treatment is recommended, with radical prostatectomy shown to be superior to watchful waiting in prospective randomized trials. The approach of choice in organ-confined disease is nerve-sparing radical prostatectomy, while neoadjuvant ADT provides no improvement in outcome variables. EBRT should be performed with a dose of at least 74 Gy in low-risk prostate cancer and 78 Gy in intermediate- or high-risk prostate cancer. For locally advanced disease, the treatment of choice is adjuvant ADT for 3 years, which is associated with superior disease-specific and overall survival.⁴²

NICE

The National Institute for Health and Care Excellence (NICE) guidelines on the diagnosis and treatment of prostate cancer recommend the following⁴³:

- For men with low-risk localized prostate cancer, offer active surveillance as the first option for those who are eligible for radical treatment;
- For men with intermediate-risk localized or locally advanced prostate cancer, offer radical prostatectomy or EBRT; consider active surveillance for those who do not wish to have immediate radical prostatectomy or EBRT;
- For men with high-risk localized or locally advanced prostate cancer, offer radical prostatectomy or EBRT when there is a realistic prospect of long-term disease control; do not offer active surveillance.

Assessing Cost-Effectiveness of Early-Stage Therapies in the Managed Care Environment

To date, the existing literature provides limited data comparing primary treatment strategies for patients with early-stage prostate cancer. The available data are limited to a few randomized trials and observational studies, and current prospective trials are not yet completed.⁴⁴ The lack of sufficient evidence from randomized trials to guide decisions in the treatment of localized prostate

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cancer creates gaps in the prostate cancer literature. More comparative effectiveness research using observational data is needed to assess the relative benefits and risks of localized prostate cancer treatments.¹⁴

Prostate Cancer Treatment Patterns

Prostate cancer places an enormous clinical and economic burden on patients and the healthcare system. The study of treatment patterns and resource utilization of various prostate cancer treatments by Crawford and colleagues indicates a high level of burden with or without active treatment. In the United States, the estimated medical costs for patients with prostate cancer were approximately \$25,000 over a 2-year period (using 2000 to 2005 claims data) even without the initiation of active treatment. The estimated costs over this period rose to more than \$56,000 with the initiation of active treatment.⁴⁵

An analysis of the Surveillance, Epidemiology, and End Results (SEER) Medicare database by Shahinian and colleagues showed that patterns of use of ADT for prostate cancer corresponded with changes in Medicare reimbursement policy. In the 1990s, Medicare policies allowed for the reimbursement of gonadotropin-releasing hormone (GnRH) agonists at 95% of the average wholesale price, which led to the displacement of orchiectomy by the use of GnRH agonists as the predominant form of ADT. Many patients received ADT for prostate cancer despite being considered unlikely to benefit from active therapy. The Medicare Modernization Act resulted in substantial changes to the drug reimbursement policy of Medicare Part B, which included drastic cuts in reimbursement for GnRH agonists. Results from the analysis by Shahinian and colleagues showed that inappropriate use of ADT declined substantially following reductions in reimbursement for GnRH agonists in 2004 and 2005.⁴⁶

Adoption of New Technologies

Concerns related to the overuse of more expensive therapies that had limited comparative effectiveness data when introduced have led to additional studies investigating the trends in adoption of IMRT. Jacobs and colleagues used SEER-Medicare data to analyze the dissemination of IMRT in patients diagnosed with prostate cancer from 2001 to 2007. The authors found a rapid adoption of IMRT, despite the lack of evidence for its relative effectiveness. With IMRT costs ranging from \$15,000 to \$20,000 higher than other standard therapies,

their analysis brings attention to the risk of overtreatment and overuse of new, unproven technology and the burden of associated healthcare costs.⁴⁷

The rapid shift to more expensive therapies over less expensive alternatives for men with prostate cancer resulted in an estimated excess in spending of \$282 million for IMRT, \$59 million for brachytherapy plus IMRT, and \$4 million for minimally invasive radical prostatectomy, according to one study. Nguyen and colleagues used SEER-Medicare data in their analysis of treatment patterns for men 65 years and older who received surgery or radiation for localized prostate cancer diagnosed from 2002 to 2005. Their findings showed increasing use of the more expensive treatment options including: minimally invasive radical prostatectomy among patients receiving surgery, IMRT among those receiving external radiation, and supplemental IMRT among those receiving brachytherapy. There was also a decline in the use of less costly traditional therapies (open radical prostatectomy, 3D conformal radiation therapy, and brachytherapy plus 3D conformal radiation therapy). The analysis also showed that patients who received the more expensive therapies also tended to have lower-stage disease.⁴⁸

Dinan and colleagues reported similar changes in treatment patterns in their retrospective claims-based analysis of Medicare beneficiaries with prostate cancer when minimally invasive radical prostatectomy and IMRT replaced older treatment modalities. The authors noted that while current guidelines do not support a change in MIP or IMRT use as a result of stage migration, these changes in treatment patterns nevertheless may have significant implications for healthcare costs.⁴⁹

Further analysis of SEER-Medicare data was conducted by Zhang and colleagues to assess the dissemination of robotic prostatectomy among Health Service Areas (HSAs) according to the degree of managed care penetration (low vs high). The authors found that the adoption and utilization of robotic prostatectomy increased over time in both HSA categories. Markets with high managed care penetration adopted robotic prostatectomy more quickly (probability 0.52 [high] vs 0.37 [low]; $P < .01$). Despite faster initial adoption, the post adoption utilization of robotic prostatectomy was lower in markets with high managed-care penetration (probability 0.52 [high] vs 0.66 [low]; $P < .01$). Results of the analysis indicate that managed care organizations have quickly adopted robotic prostatectomy, but with constrained utilization.²⁸

Prostate Cancer Treatment Costs

Snyder and colleagues examined how initial treatment choice for prostate cancer affects short-term and long-term costs in a retrospective, longitudinal cohort study using SEER-Medicare data. The authors divided costs into initial treatment (months -1 to 12), long-term (each 12 months thereafter), and total (months -1 to 60). Initial treatment costs considered perioperative outcomes, surgical complications, and acute radiation toxicity, while long-term costs reflected oncologic or QOL outcomes. Results of the study showed that watchful waiting was associated with the lowest initial treatment and 5-year total costs (\$4270 and \$9130, respectively). The highest initial treatment costs were associated with combination treatment (ADT plus radiation therapy) and surgery (\$17,474 and \$15,197, respectively). The highest 5-year total costs were for ADT (\$26,896), combination treatment (ADT plus radiation therapy) (\$25,097), and surgery (\$19,214).⁵⁰

Perlroth and colleagues analyzed healthcare claims data (1998 to 2006) to calculate costs associated with the initial management of localized prostate cancer and to estimate potential savings from a shift from current treatment patterns to conservative management strategies, including active surveillance for the initial treatment of localized prostate cancer. Combination treatments were associated with the highest additional costs over conservative management (\$63,500), followed by IMRT (\$48,550), primary ADT (\$37,500), brachytherapy (\$28,600), EBRT (\$18,900), and radical prostatectomy (\$15,200). The authors calculated potential annual savings of \$2.9 billion to \$3.25 billion in US healthcare expenditures with the use of initial conservative management versus all other active treatment options. The potential savings associated with the use of initial conservation management versus IMRT were estimated at \$680 million to \$930 million. Other potential savings were estimated at \$555 million with foregoing ADT, \$630 million with reducing adjuvant ADT in addition to local therapies, and \$620 million to \$650 million with using single treatments rather than combination local treatment. The adoption of conservative management strategies for the initial management of patients with localized prostate cancer represents substantial savings of up to 30% of total costs.⁵¹

Comparative Studies in Prostate Cancer

Xiong and colleagues conducted a systematic review with Bayesian network meta-analysis to evaluate the comparative efficacy and safety of different treatments

for patients with localized prostate cancer. The authors integrated evidence from direct and indirect comparisons for prostatectomy, EBRT, observational management, and cryotherapy. Results of the meta-analysis showed no evidence of superiority for any of the compared treatments in terms of all-cause mortality after 5 years. Safety findings indicated that cryotherapy was associated with less gastrointestinal and genitourinary toxicity than radiation therapy.⁵²

Hayes and colleagues conducted a cost-effectiveness analysis comparing observation (active surveillance or watchful waiting) versus initial treatment (brachytherapy, IMRT, or radical prostatectomy) for patients with localized prostate cancer. The authors analyzed recent trial data generated through a systematic review updated through June 2012 and from the PIVOT trial. Results of the analysis supported the benefits of observation over initial treatment in terms of efficacy and cost. Watchful waiting resulted in 2 additional months of quality-adjusted life expectancy and a savings of \$15,374 versus active surveillance for men aged 65 years. The benefits associated with watchful waiting over active surveillance for men aged 75 years were an improvement in quality-adjusted life expectancy of 2 additional months and a savings of \$11,746.⁵³

Cooperberg and colleagues performed a comprehensive lifetime cost-utility analysis to determine costs and quality-adjusted outcomes between surgery and radiation therapy at various strata of disease risk. Results of the analysis showed that, although there was no difference in survival between surgery and radiation therapy, there was a significant difference in cost. Radiation therapy was significantly more expensive than surgery ($P = .008$); costs ranged from approximately \$20,000 for robotic-assisted prostatectomy to \$50,000 for combined radiation for high-risk disease. The authors found that treatment options resulted in small differences in outcomes and substantial differences in payer and patient costs.⁵⁴

PROs and QOL Outcomes

Rising healthcare costs have resulted in greater interest in measuring outcomes in relation to treatment costs. At the same time, the reporting of patient outcomes and quality measures continues to be hampered by several limitations. Most data on PROs are from single institution trials of a single therapy. Biases in reporting lead to an overrepresentation of favorable outcomes and a corresponding underrepresentation of negative outcomes in published work.

Reports

Efficace and colleagues conducted a systematic literature review to investigate the methodological quality of PRO assessment in RCTs of prostate cancer and to estimate the impact of PRO assessment on clinical decision making. The authors found that the quality of PRO reporting has markedly improved between January 2004 and March 2012, and estimated that at least one-fifth of the current literature provides sufficient details to allow health policy makers and physicians to make critical appraisals of results. The findings of the investigation by Efficace and colleagues reflect the ongoing need for high-quality PRO data to measure the impact of treatment and to inform patient-centered care and clinical and health policy decisions.⁵⁵

Johansson and colleagues analyzed long-term QOL after treatment of clinically localized disease in the Scandinavian randomized controlled trial (SPCG-4) comparing radical prostatectomy with watchful waiting. The authors reported a general reduction in QOL associated with the diagnosis of prostate cancer, regardless of the type of treatment given.⁵⁶ Contrary to the results from the PIVOT trial, the follow-up data from the SPCG-4 trial confirmed substantial reduction in mortality after radical prostatectomy.⁵⁷

The phase 3 study by Warde and colleagues compared ADT with or without radiation therapy. Findings showed an overall survival advantage in the radiation therapy arm, with no PRO differences at 36 months. Declines in overall QOL and physical function scores occurred in both groups, reflecting the expected outcome with ADT suppression. The combination of ADT and radiation therapy produced greater benefits in terms of lowering overall and disease-specific mortality while resulting in a manageable adverse event profile and no difference in PRO compared with ADT alone.⁵⁸

Acar and colleagues performed a prospective database study to investigate the QOL following different treatment modalities for low-risk prostate cancer, including brachytherapy, robot-assisted laparoscopic prostatectomy (RALP), and active surveillance (AS). Validated questionnaires were used to compare QOL outcomes of patients with localized prostate cancer with their baseline QOL measures before treatment. The brachytherapy group showed a significant decrease in the following QOL domain scores: voiding complaints ($P = .010$), use of incontinence aids ($P = .011$), sexual functioning ($P = .011$), and erectile function ($P \leq .001$). The RALP group showed a significant decrease in sexual function ($P \leq .001$), incontinence ($P \leq .001$), and erectile function ($P \leq .00$). Decreases in

sexual function were less common in the brachytherapy group (59%) compared with the RALP group (71%). In the AS group, 30% of men reported a decrease in erectile function score during follow-up. None of the groups (AS, brachytherapy, or RALP) reported a significant decrease in general QOL.⁵⁹

Conclusion

The treatment of localized prostate cancer is a key area of uncertainty, especially concerning the relative merits of observational management and active treatment approaches. Prostate cancer is a long-term condition with multiple therapeutic options for which there are limited comparative effectiveness and cost-effectiveness data. Additional studies are needed to evaluate clinical and economic benefits and to demonstrate improvement in patient outcomes associated with prostate cancer therapies.

Author affiliation: Carolina Urologic Research Center (CURC), Atlantic Urology Clinics, Myrtle Beach, SC.

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Address correspondence to: E-mail: nshore@asuro.com.

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