This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the treatment of prostate cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

This summary is reviewed regularly and updated as necessary by the PDQ Adult Treatment Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

General Information About Prostate Cancer

The median age at diagnosis of carcinoma of the prostate is 66 years.[1] Prostate cancer may be cured when localized, and it frequently responds to treatment when widespread. The rate of tumor growth varies from very slow to moderately rapid, and some patients may have prolonged survival even after the cancer has metastasized to distant sites, such as bone. The 5-year relative survival rate for men diagnosed in the United States from 2001 to 2007 with local or regional disease was 100%, and the rate for distant disease was 28.7%; a 99% survival rate was observed for all stages combined.[2] The approach to treatment is influenced by age and coexisting medical problems. Side effects of various forms of treatment should be considered in selecting appropriate management.

Many patients—especially those with localized tumors—may die of other illnesses without ever having suffered disability from the cancer, even if managed conservatively without an attempt at curative therapy.[3,4] In part, these favorable outcomes are likely the result of widespread screening with the prostate-specific antigen (PSA) test, which can identify patients with asymptomatic tumors that have little or no lethal potential.[5] There is a large number of these clinically indolent tumors, estimated from autopsy series of men dying of causes unrelated to prostate cancer to be in the range of 30% to 70% of men older than 60 years.[6,7]

Because diagnostic methods have changed over time, any analysis of survival after treatment of prostate cancer and comparison of the various treatment strategies is complicated by the evidence of increasing diagnosis of nonlethal tumors. Nonrandomized comparisons of treatments may be confounded not only by patient selection factors but also by time trends.

For example, a population-based study in Sweden showed that, from 1960 to the late 1980s, before the use of PSA for screening purposes, long-term relative survival rates after the diagnosis of prostate cancer improved substantially as more sensitive methods of diagnosis were introduced. This occurred despite the use of watchful waiting or active surveillance or palliative hormonal treatment as the most common treatment strategies for localized prostate cancer during the entire era (<150 radical prostatectomies per year were performed in Sweden during the late 1980s). The investigators estimated that, if all prostate cancers diagnosed between 1960 and 1964 were of the lethal variety, then at least 33% of cancers diagnosed between 1980 and 1984 were of the nonlethal variety. [8][Level of evidence: 3iB] With the advent of PSA screening as the most common method of detection in the United States, the ability to diagnose nonlethal prostate cancers has further increased.

Another issue complicating comparisons of outcomes among nonconcurrent series of patients is the possibility of changes in criteria for the histologic diagnosis of prostate cancer.[9] This phenomenon creates a statistical artifact that can produce a false sense of therapeutic accomplishment and may also lead to more aggressive therapy.

Controversy exists regarding the value of screening, the most appropriate staging evaluation, and the optimal treatment of each stage of the disease.[10-14]
Incidence and Mortality

Estimated new cases and deaths from prostate cancer in the United States in 2016:[15][A Snapshot of Prostate Cancer]

- New cases: 180,890.
- Deaths: 26,120.

Anatomy

Anatomy of the male reproductive and urinary systems.

Screening

The issue of prostate cancer screening is controversial. In the United States, most prostate cancers are diagnosed as a result of screening, either with a PSA blood test or, less frequently, with a digital rectal examination. Randomized trials have yielded conflicting results.[16-18] Systematic literature reviews and meta-analyses have reported no clear evidence that screening for prostate cancer decreases the risk of death from prostate cancer, or that the benefits outweigh the harms of screening.[19,20]

(Refer to the PDQ summary on Prostate Cancer Screening for a detailed summary of evidence regarding the benefits and harms of screening for prostate cancer.)

Pathology

More than 95% of primary prostate cancers are adenocarcinomas. Prostate adenocarcinomas are frequently multifocal and heterogeneous in patterns of differentiation. Prostatic intraepithelial neoplasia ([PIN] noninvasive atypical epithelial cells within benign appearing acini) is often present in association with prostatic adenocarcinoma. PIN is subdivided into low grade and high grade. The high-grade form may be a precursor for adenocarcinoma.[21]

A number of rare tumors account for the remaining few percentages of cases. These include the following:

- Small-cell tumors.
- Intralobular acinar carcinomas.
Ductal carcinomas.

Clear cell carcinomas.

Mucinous carcinomas.[22]

**Gleason score**

The histologic grade of prostate adenocarcinomas is usually reported according to one of the variations of the Gleason scoring system, which provides a useful, albeit crude, adjunct to tumor staging in determining prognosis.[22] The Gleason score is calculated based on the dominant histologic grades, from grade 1 (well differentiated) to grade 5 (very poorly differentiated). The classical score is derived by adding the two most prevalent pattern grades, yielding a score ranging from 2 to 10. Because there is some evidence that the least-differentiated component of the specimen may provide independent prognostic information, the score is often provided by its separate components (e.g., Gleason score 3 + 4 = 7; or 4 + 3 = 7).[23]

There is evidence that, over time, pathologists have tended to award higher Gleason scores to the same histologic patterns, a phenomenon sometimes termed “grade inflation.”[24,25] This phenomenon complicates comparisons of outcomes in current versus historical patient series. For example, prostate biopsies from a population-based cohort of 1,858 men diagnosed with prostate cancer from 1990 through 1992 were re-read in 2002 to 2004.[24,25] The contemporary Gleason score readings were an average of 0.85 points higher (95% confidence interval, 0.79–0.91; *P* < .001) than the same slides read a decade earlier. As a result, Gleason-score standardized prostate cancer mortality rates for these men were artificially improved from 2.08 to 1.50 deaths per 100 person years—a 28% decrease even though overall outcomes were unchanged.

**Molecular markers**

A number of tumor markers have been reported to be associated with the outcome of prostate cancer patients.[21,22] These include:

- Markers of apoptosis including Bcl-2, Bax.
- Markers of proliferation rate, such as Ki67.
- p53 mutation or expression.
- p27.
- E-cadherin.
- Microvessel density.
- DNA ploidy.
- p16.
- PTEN gene hypermethylation and allelic losses.

However, none of these has been prospectively validated; and they are not a part of the routine management of patients.

**Clinical Presentation**

In the United States, most prostate cancers are diagnosed as a result of screening; therefore, symptoms of cancer are infrequent at the time of diagnosis.[22] Nevertheless, local growth of the tumor may produce symptoms of urinary obstruction such as:

- Decreased urinary stream.
- Urgency.
- Hesitancy.
- Nocturia.
- Incomplete bladder emptying.

These symptoms are nonspecific and more indicative of benign prostatic hyperplasia than cancer.

Although rare in the current era of widespread screening, prostate cancer may also present with symptoms of metastases, such as bone pain, pathologic fractures, or symptoms caused by bone marrow involvement.

**Diagnostic Evaluation**

Needle biopsy is the most common method used to diagnose prostate cancer. Most urologists now perform a transrectal biopsy using a biopsy gun with ultrasound guidance. Over the years, there has been a trend toward taking eight to ten or more biopsy samples from several areas of the prostate with a consequent increased yield of cancer detection after an elevated PSA blood test.[22] Less frequently, a transperineal, ultrasound-guided approach can be used in patients who may be at increased risk of complications caused by using a transrectal approach.[26]

Prophylactic antibiotics, especially fluoroquinolones, are often used before transrectal needle biopsies. There are reports of increasing rates of sepsis, particularly with fluoroquinolone-resistant *E. coli*, and hospitalization after the procedure.[27,28] Therefore, men undergoing transrectal biopsy should be told to seek medical attention immediately if they experience fever after biopsy.

**Prognostic Factors**

The survival of patients with prostate cancer is related to several factors, including the following:[29-33]

- **Extent of tumor.**
- **Histologic grade of tumor.**
- **Patient's age and health.**
- **Prostate-specific antigen (PSA) level.**

(Refer to the Surveillance, Epidemiology, and End Results' 5-year and 10-year survival rates.)

**Extent of tumor**

When the cancer is confined to the prostate gland, long-term prognosis is excellent. Patients with locally advanced cancer are not usually curable, but 5-year survival is still very good. If prostate cancer has spread to distant organs, current therapy will not cure it. Median survival is usually 1 to 3 years, and most of these patients will die of prostate cancer. Even in this group of patients, indolent clinical courses lasting for many years may be observed.

**Histologic grade of tumor**

Poorly differentiated tumors are more likely to have metastasized before diagnosis and are associated with a poorer prognosis. The most commonly used method to report tumor differentiation is the Gleason score. (Refer to the Pathology section of the General Information About Prostate Cancer section of this summary for more information.)

**Patient's age and health**

Any benefits of definitive local therapy with curative intent may take years to emerge. Therefore, therapy with curative intent is usually reserved for men with a sufficiently long life expectancy. For example, radical prostatectomy is often reserved for men with an estimated life expectancy of at least 10 years.

**Prostate-specific antigen (PSA) level**

PSA, an organ-specific marker, is often used as a tumor marker.[31,32,34-39] The higher the level of PSA at baseline, the higher is the risk for metastatic disease or subsequent disease progression. However, it is an imprecise marker of risk.

For example, baseline PSA and rate of PSA change were associated with subsequent metastasis or prostate cancer...
death in a cohort of 267 men with clinically localized prostate cancer who were managed by watchful waiting or active surveillance in the control arm of a randomized trial comparing radical prostatectomy with watchful waiting or active surveillance.[40,41] Nevertheless, the accuracy of classifying men into groups whose cancer remained indolent versus those whose cancer progressed was poor at all examined cut points of PSA or PSA rate of change.

**Serum acid phosphatase levels**

Elevations of serum acid phosphatase are associated with poor prognosis in both localized and disseminated disease. However, serum acid phosphatase levels are not incorporated into the American Joint Committee on Cancer's (AJCC) staging system for prostate cancer.[34]

**Use of nomograms as a prognostic tool**

Several nomograms have been developed to predict outcomes either before radical prostatectomy [42-45] or after radical prostatectomy [46,47] with intent to cure. Preoperative nomograms are based on clinical stage, PSA level, Gleason score, and the number of positive and negative prostate biopsy cores. One independently validated nomogram demonstrated increased accuracy in predicting biochemical recurrence-free survival by including preoperative plasma levels of transforming growth factor B1 and interleukin-6 soluble receptor.[48,49]

Postoperative nomograms add pathologic findings, such as capsular invasion, surgical margins, seminal vesicle invasion, and lymph node involvement. The nomograms, however, were developed at academic centers and may not be as accurate when generalized to nonacademic hospitals, where the majority of patients are treated.[50,51] In addition, the nomograms use nonhealth (intermediate) outcomes, such as PSA rise or pathologic surgical findings, and subjective endpoints, such as the physician's perceived need for additional therapy. In addition, the nomograms may be affected by changing methods of diagnosis or neoadjuvant therapy.[43]

**Follow-up After Treatment**

The optimal follow-up strategy for men treated for prostate cancer is uncertain. Men should be interviewed and examined for symptoms or signs of recurrent or progressing disease, as well as side effects of therapy that can be managed by changes in therapy. However, using surrogate endpoints for clinical decision making is controversial, and the evidence that changing therapy based on such endpoints translates into clinical benefit is weak. Often, rates of PSA change are thought to be markers of tumor progression. However, even though a tumor marker or characteristic may be consistently associated with a high risk of prostate cancer progression or death, it may be a very poor predictor and of very limited utility in making therapeutic decisions.

Although the PSA test is nearly universally used to follow patients, the diversity of recommendations on the provision of follow-up care reflects the current lack of research evidence on which to base firm conclusions. A systematic review of international guidelines highlights the need for robust primary research to inform future evidence-based models of follow-up care for men with prostate cancer.[52]

Preliminary data from a retrospective cohort of 8,669 patients with clinically localized prostate cancer treated with either radical prostatectomy or radiation therapy suggested that short post-treatment PSA doubling time (<3 months in this study) fulfills some criteria as a surrogate endpoint for all-cause mortality and prostate cancer-specific mortality after surgery or radiation therapy.[53]

Likewise, a retrospective analysis (SWOG-S9916 [NCT00004001]) showed that PSA declines of 20% to 40% (but not 50%) at 3 months and 30% or more at 2 months after initiation of chemotherapy for hormone-independent prostate cancer, and fulfilled several criteria of surrogacy for overall survival (OS).[54]

These observations should be independently confirmed in prospective study designs and may not apply to patients treated with hormonal therapy. In addition, there are no standardized criteria of surrogacy or standardized cutpoints for adequacy of surrogate endpoints, even in prospective trials.[55]

**Follow-up after radical prostatectomy**

After radical prostatectomy, a detectable PSA level identifies patients at elevated risk of local treatment failure or metastatic disease:[36] however, a substantial proportion of patients with an elevated or rising PSA level after surgery remain clinically free of symptoms for extended periods of time.[56] Biochemical evidence of failure on the basis of
elevated or slowly rising PSA alone, therefore, may not be sufficient to initiate additional treatment.

For example, in a retrospective analysis of nearly 2,000 men who had undergone radical prostatectomy with curative intent and who were followed for a mean of 5.3 years, 315 men (15%) demonstrated an abnormal PSA of 0.2 ng/ml or higher, which is considered evidence of biochemical recurrence. Among these 315 men, 103 (34%) developed clinical evidence of recurrence. The median time to the development of clinical metastasis after biochemical recurrence was 8 years. After the men developed metastatic disease, the median time to death was an additional 5 years.[57]

**Follow-up after radiation therapy**

For patients treated with radiation therapy, the combination of clinical tumor stage, Gleason score, and pretreatment PSA level is often used to estimate the risk of relapse.[58][Level of evidence: 3dii] As is the case after prostatectomy, PSA is often followed for signs of tumor recurrence after radiation therapy. After radiation therapy with curative intent, persistently elevated or rising PSA may be a prognostic factor for clinical disease recurrence; however, reported case series have used a variety of definitions of PSA failure. Criteria have been developed by the American Society for Therapeutic Radiology and Oncology Consensus Panel.[59,60] It is difficult to base decisions about initiating additional therapy on biochemical failure alone. The implication of the various definitions of PSA failure for OS is not known, and, as in the surgical series, many biochemical relapses (rising PSA only) may not be clinically manifested in patients treated with radiation therapy.[61,62]

**Follow-up after hormonal therapy**

After hormonal therapy, reduction of PSA to undetectable levels provides information regarding the duration of progression-free status; however, decreases in PSA of less than 80% may not be very predictive.[31] Because PSA expression itself is under hormonal control, androgen deprivation therapy can decrease the serum level of PSA independent of tumor response. Clinicians, therefore, cannot rely solely on the serum PSA level to monitor a patient’s response to hormonal therapy; they must also follow clinical criteria.[63]

**Related Summaries**

Other PDQ summaries containing information related to prostate cancer include the following:

- Genetics of Prostate Cancer
- Prostate Cancer, Nutrition, and Dietary Supplements
- Prostate Cancer Prevention
- Prostate Cancer Screening

**References**

22. Chodak GW, Thisted RA, Gerber GS, et al.: Results of conservative management of clinically localized prostate...

Stage Information for Prostate Cancer

Staging Tests

Most men are diagnosed with prostate cancer at an early clinical stage and do not have detectable metastases. Therefore, they generally do not have to undergo staging tests, such as a bone scan, computed tomography (CT), or magnetic resonance imaging (MRI). However, staging studies are done if there is clinical suspicion of metastasis, such as bone pain; local tumor spread beyond the prostate capsule; or a substantial risk of metastasis (prostate-specific antigen [PSA] >20 ng/ml and Gleason score >7).[1]

Tests used to determine stage include the following:

1. Radionuclide bone scans.
2. Serum PSA level.
3. MRI.
4. Pelvic lymph node dissection (PLND).
5. Transrectal or transperineal biopsy.
6. Transrectal ultrasound (TRUS).
7. CT scans.

Radionuclide bone scans

A radionuclide bone scan is the most widely used test for metastasis to the bone, which is the most common site of distant tumor spread.

Serum prostate-specific antigen (PSA) level

Serum PSA can predict the results of radionuclide bone scans in newly diagnosed patients.
In one series, only 2 of 852 patients (0.23%) with a PSA of less than 20 ng/ml had a positive bone scan in the absence of bone pain.[2]

In another series of 265 prostate cancer patients, 0 of 23 patients with a PSA of less than 4 ng/ml had a positive bone scan, and 2 of 114 patients with a PSA of less than 10 ng/ml had a positive bone scan.[3]

Magnetic resonance imaging (MRI)

Although MRI has been used to detect extracapsular extension of prostate cancer, a positive-predictive value of about 70% and considerable interobserver variation are problems that make its routine use in staging uncertain.[4] Ultrasound and MRI, however, can reduce clinical understaging and thereby improve patient selection for local therapy. MRI with an endorectal coil appears to be more accurate for identification of organ-confined and extracapsular disease, especially when combined with spectroscopy.[1] MRI is a poor tool for evaluating nodal disease.

MRI is more sensitive than radionuclide bone scans in the detection of bone metastases, but it is impractical for evaluating the entire skeletal system.

Pelvic lymph node dissection (PLND)

PLND remains the most accurate method to assess metastasis to the pelvic nodes, and laparoscopic PLND has been shown to accurately assess pelvic nodes as effectively as an open procedure.[5]

The determining factor in deciding whether any type of PLND is indicated is when definitive therapy may be altered. For example, radical prostatectomy is generally reserved for men without lymph node metastasis. Likewise, preoperative seminal vesicle biopsy may be useful in patients with palpable nodules who are being considered for radical prostatectomy (unless they have a low Gleason score) because seminal vesicle involvement could affect the choice of primary therapy and predicts for pelvic lymph node metastasis.[6]

In patients with clinically localized (stage I or stage II) prostate cancer, Gleason pathologic grade and enzymatic serum prostatic acid phosphatase values (even within normal range) predict the likelihood of capsular penetration, seminal vesicle invasion, or regional lymph node involvement.[7] Analysis of a series of 166 patients with clinical stage I or stage II prostate cancer undergoing radical prostatectomy revealed an association between Gleason biopsy score and the risk of lymph node metastasis found at surgery. The risks of nodal metastasis for patients grouped according to their Gleason biopsy score was 2%, 13%, and 23% for Gleason scores of 5, 6, and 8, respectively.[8]

Whether to subject all patients to a PLND is debatable, but in patients undergoing a radical retropubic prostatectomy, nodal status is usually ascertained as a matter of course. In patients who are undergoing a radical perineal prostatectomy in whom the PSA value is less than 20 ng/ml and the Gleason sum is low, however, evidence is mounting that a PLND is probably unnecessary, especially in patients whose malignancy was not palpable but detected on ultrasound.[7,9]

Transrectal or transperineal biopsy

The most common means to establish a diagnosis and determine the Gleason score in cases of suspected prostate cancer is by needle biopsy. Most urologists now perform a transrectal biopsy using a bioptic gun with ultrasound guidance. Over the years, there has been a trend toward taking eight to ten or more biopsy samples at the same time.[1] Less frequently, a transperineal, ultrasound-guided approach can be used for those patients who may be at increased risk of complications from a transrectal approach.[10]

Transrectal ultrasound (TRUS)

TRUS may facilitate diagnosis by directing needle biopsy; however, ultrasound is operator dependent and does not assess lymph node size.

A prospective multi-institutional study of preoperative TRUS in men with clinically localized prostate cancer eligible for radical prostatectomy showed that TRUS was no better than digital rectal examination in predicting extracapsular tumor extension or seminal vesicle involvement.[11]
Computed tomography (CT) scans
CT scans can detect grossly enlarged lymph nodes but poorly define intraprostatic features;[12] therefore, it is not reliable for the staging of pelvic node disease when compared with surgical staging.[13]

Staging Systems
Historically, two systems have been in common use for the staging of prostate cancer.

- In 1975, the Jewett system (stage A through stage D) was described and has since been modified.[14] This staging system is no longer in common use, but older studies and publications may refer to it.

- In 1997, the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer adopted a revised tumor, nodes, metastasis (TNM) system, which used the same broad T-stage categories as the Jewett system but included subcategories of T stage, such as a stage to describe patients diagnosed through PSA screening. This revised TNM system more precisely stratifies newly diagnosed patients. In 2010, the AJCC updated the TNM classification for prostate cancer.[15]

AJCC Stage Groupings and TNM Definitions
The AJCC has designated staging by TNM classification.[15]
Prostate cancer staging.

### Table 1. Definitions of TNM Stage I

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1a, N0, M0, G1</td>
<td>T1a = Tumor incidental histologic finding in ≤5% of tissue resected.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N0 = No regional lymph node metastasis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M0 = No distant metastasis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).</td>
</tr>
</tbody>
</table>

T = Primary tumor; N = Regional lymph nodes; M = Distant metastasis; G = Histopathologic grade.


The explanation for superscript a is at the end of Table 4.
<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>T1a, N0, M0, G2–4</td>
<td>T1a = Tumor incidental histologic finding in ≤5% of tissue resected. N0 = No regional lymph node metastasis. M0 = No distant metastasis. G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6). G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).</td>
</tr>
<tr>
<td>IIA</td>
<td>T1b, N0, M0, any G</td>
<td>T1b = Tumor incidental histologic finding in &gt;5% of tissue resected. N0 = No regional lymph node metastasis. M0 = No distant metastasis. GX = Grade cannot be assessed. G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4). G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6). G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).</td>
</tr>
<tr>
<td>IIA</td>
<td>T1c, N0, M0, any G</td>
<td>T1c = Tumor identified by needle biopsy (e.g., because of elevated PSA). N0 = No regional lymph node metastasis. M0 = No distant metastasis. GX = Grade cannot be assessed. G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4). G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6). G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).</td>
</tr>
<tr>
<td>IIB</td>
<td>T1, N0, M0, any G</td>
<td>T1 = Clinically inapparent tumor neither palpable nor visible by imaging. N0 = No regional lymph node metastasis. M0 = No distant metastasis. GX = Grade cannot be assessed. G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4). G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6). G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).</td>
</tr>
<tr>
<td>IIB</td>
<td>T2, N0, M0, any G</td>
<td>T2 = Tumor confined within prostate. N0 = No regional lymph node metastasis. M0 = No distant metastasis. GX = Grade cannot be assessed. G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4). G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6). G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).</td>
</tr>
</tbody>
</table>

T = Primary tumor; N = Regional lymph nodes; M = Distant metastasis; G = Histopathologic grade.
Table 3. Definitions of TNM Stage III

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>T3, N0, M0, any G</td>
<td>T3 = Tumor extends through the prostate capsule.(^c)&lt;br&gt;N0 = No regional lymph node metastasis.&lt;br&gt;M0 = No distant metastasis.(^a)&lt;br&gt;GX = Grade cannot be assessed.&lt;br&gt;G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).&lt;br&gt;G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).&lt;br&gt;G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).</td>
</tr>
</tbody>
</table>

T = Primary tumor; N = Regional lymph nodes; M = Distant metastasis; G = Histopathologic grade.

Table 4. Definitions of TNM Stage IV

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>T4, N0, M0, any G</td>
<td>T4 = Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.&lt;br&gt;N0 = No regional lymph node metastasis.&lt;br&gt;M0 = No distant metastasis.(^a)&lt;br&gt;GX = Grade cannot be assessed.&lt;br&gt;G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).&lt;br&gt;G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).&lt;br&gt;G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).</td>
</tr>
<tr>
<td></td>
<td>Any T, N1, M0, any G</td>
<td>TX = Primary tumor cannot be assessed.&lt;br&gt;T0 = No evidence of primary tumor.&lt;br&gt;T1 = Clinically inapparent tumor not palpable or visible by imaging.&lt;br&gt;T1a = Tumor incidental histologic finding in ≤5% of tissue resected.&lt;br&gt;T1b = Tumor incidental histologic finding in &gt;5% of tissue resected.&lt;br&gt;T1c = Tumor identified by needle biopsy (e.g., because of elevated PSA).&lt;br&gt;T2 = Tumor confined within prostate.(^b)&lt;br&gt;T2a = Tumor involves ≤50% of one lobe.&lt;br&gt;T2b = Tumor involves &gt;50% of one lobe but not both lobes.&lt;br&gt;T2c = Tumor involves both lobes.&lt;br&gt;T3 = Tumor extends through the prostate capsule.(^c)</td>
</tr>
<tr>
<td>Stage</td>
<td>TNM Description</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td>Any T, any N, M1, any G</td>
<td>TX = Primary tumor cannot be assessed.</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor.</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Clinically inapparent tumor not palpable or visible by imaging.</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor incidental histologic finding in ≤5% of tissue resected.</td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor incidental histologic finding in &gt;5% of tissue resected.</td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor identified by needle biopsy (e.g., because of elevated PSA).</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumor confined within prostate.</td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor involves ≤50% of one lobe.</td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor involves &gt;50% of one lobe but not both lobes.</td>
<td></td>
</tr>
<tr>
<td>T2c</td>
<td>Tumor involves both lobes.</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumor extends through the prostate capsule.</td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>Extracapsular extension (unilateral or bilateral).</td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>Tumor invades seminal vesicle(s).</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumor is fixed or invades adjacent structures other than seminal vesicles such as the bladder, external sphincter, rectum, levator muscles, and/or pelvic wall.</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis.</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in regional lymph node(s).</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in regional lymph node(s).</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in regional lymph node(s).</td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis.</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis.</td>
<td></td>
</tr>
<tr>
<td>M1a</td>
<td>Nonregional lymph node(s).</td>
<td></td>
</tr>
<tr>
<td>M1b</td>
<td>Bone(s).</td>
<td></td>
</tr>
<tr>
<td>M1c</td>
<td>Other site(s) with or without bone disease.</td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>Well differentiated (slight anaplasia) (Gleason score of 2–4).</td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).</td>
<td></td>
</tr>
<tr>
<td>G3–4</td>
<td>Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).</td>
<td></td>
</tr>
</tbody>
</table>
T = Primary tumor; N = Regional lymph nodes; M = Distant metastasis; G = Histopathologic grade; p = Pathologic.


aWhen more than one site of metastasis is present, the most advanced category (pM1c) is used.

bTumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.

cInvasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.

Table 5. Pathologic (pT)a, b

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT2</td>
<td>Organ confined.</td>
</tr>
<tr>
<td>pT2a</td>
<td>Unilateral, ≤½ of one side.</td>
</tr>
<tr>
<td>pT2b</td>
<td>Unilateral, involving &gt;¼ of side but not both sides.</td>
</tr>
<tr>
<td>pT2c</td>
<td>Bilateral disease.</td>
</tr>
<tr>
<td>pT3</td>
<td>Extraprostatic extension.</td>
</tr>
<tr>
<td>pT3a</td>
<td>Extraprostatic extension or microscopic invasion of bladder neck.</td>
</tr>
<tr>
<td>pT3b</td>
<td>Seminal vesicle invasion.</td>
</tr>
<tr>
<td>pT4</td>
<td>Invasion of rectum, levator muscles, and/or pelvic wall.</td>
</tr>
</tbody>
</table>

p = Pathologic; T = Primary tumor.


aThere is no pathologic T1 classification.

bPositive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

Table 6. Prognostic Factors (Site-Specific Factors)

<table>
<thead>
<tr>
<th>Site-Specific Factors</th>
<th>Testing and Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required for staging</td>
<td>PSA.</td>
</tr>
<tr>
<td></td>
<td>Gleason score.</td>
</tr>
<tr>
<td>Clinically significant</td>
<td>Gleason primary and secondary patterns.</td>
</tr>
<tr>
<td></td>
<td>Gleason tertiary pattern.</td>
</tr>
<tr>
<td></td>
<td>Clinical staging procedures performed.</td>
</tr>
<tr>
<td></td>
<td>Number of biopsy cores examined.</td>
</tr>
<tr>
<td></td>
<td>Number of biopsy cores positive for cancer.</td>
</tr>
</tbody>
</table>


Table 7. Histologic Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason X</td>
<td>Gleason score cannot be processed.</td>
</tr>
<tr>
<td>Gleason ≤6</td>
<td>Well differentiated (slight anaplasia).</td>
</tr>
<tr>
<td>Gleason 7</td>
<td>Moderately differentiated (moderate anaplasia).</td>
</tr>
</tbody>
</table>
Table 8. Treatment Options by Stage for Prostate Cancer

Local treatment modalities are associated with prolonged disease-free survival (DFS) for many patients with localized prostate cancer but are rarely curative in patients with locally extensive tumors. Because of clinical understaging using current diagnostic techniques, even when the cancer appears clinically localized to the prostate gland, some patients develop disseminated tumors after local therapy with surgery or radiation. Metastatic prostate cancer is currently not curable.

Treatment options for each stage of prostate cancer are presented in Table 8.
<table>
<thead>
<tr>
<th>Stage (TNM Staging Criteria)</th>
<th>Standard Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I Prostate Cancer</td>
<td>Watchful waiting or active surveillance</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
</tr>
<tr>
<td></td>
<td>External-beam radiation therapy (EBRT)</td>
</tr>
<tr>
<td></td>
<td>Interstitial implantation of radioisotopes</td>
</tr>
<tr>
<td>Stage II Prostate Cancer</td>
<td>Watchful waiting or active surveillance</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
</tr>
<tr>
<td></td>
<td>EBRT with or without hormonal therapy</td>
</tr>
<tr>
<td></td>
<td>Interstitial implantation of radioisotopes</td>
</tr>
<tr>
<td>Stage III Prostate Cancer</td>
<td>EBRT with or without hormonal therapy</td>
</tr>
<tr>
<td></td>
<td>Hormonal manipulations (orchiectomy or luteinizing hormone-releasing hormone [LH-RH] agonist)</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy with or without EBRT</td>
</tr>
<tr>
<td></td>
<td>Watchful waiting or active surveillance</td>
</tr>
<tr>
<td>Stage IV Prostate Cancer</td>
<td>Hormonal manipulations</td>
</tr>
<tr>
<td></td>
<td>Bisphosphonates</td>
</tr>
<tr>
<td></td>
<td>EBRT with or without hormonal therapy</td>
</tr>
<tr>
<td></td>
<td>Palliative radiation therapy</td>
</tr>
<tr>
<td></td>
<td>Palliative surgery with transurethral resection of the prostate (TURP)</td>
</tr>
<tr>
<td></td>
<td>Watchful waiting or active surveillance</td>
</tr>
<tr>
<td>Recurrent Prostate Cancer</td>
<td>Hormone therapy</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy for hormone-resistant prostate cancer</td>
</tr>
<tr>
<td></td>
<td>Immunotherapy</td>
</tr>
<tr>
<td></td>
<td>Radiopharmaceutical therapy/alpha emitter radiation</td>
</tr>
</tbody>
</table>

EBRT = external-beam radiation therapy; LH-RH = luteinizing hormone-releasing hormone; TURP = transurethral resection of the prostate.

**Watchful Waiting or Active Surveillance**

Asymptomatic patients of advanced age or with concomitant illness may warrant consideration of careful observation without immediate active treatment.[1,2] Watch and wait, observation, expectant management, and active surveillance are terms indicating a strategy that does not employ immediate therapy with curative intent.

Watchful waiting and active surveillance are the most commonly used terms, and the literature does not always clearly distinguish them, making the interpretation of results difficult. The general concept of watchful waiting is patient follow-up with the application of palliative care as needed to alleviate symptoms of tumor progression. There is no planned attempt at curative therapy at any point in follow-up. For example, transurethral resection of the prostate (TURP) or hormonal therapy may be used to alleviate tumor-related urethral obstruction should there be local tumor growth; hormonal therapy or bone radiation might be used to alleviate pain from metastases. Radical prostatectomy has been compared with watchful waiting or active surveillance in men with early-stage disease (i.e., clinical stages T1b, T1c, or T2).[3] (Refer to the Radical Prostatectomy section in the Treatment Option Overview for Prostate Cancer section of this summary for more information.)

In contrast, the strategy behind active surveillance is to defer therapy for clinically localized disease but regularly follow the patient and initiate local therapy with curative intent if there are any signs of local tumor progression.[4-7] The idea is to avoid the morbidity of therapy in men who have indolent or nonprogressive disease but preserve the
ability to cure them should the tumor progress. Active surveillance usually involves:

- Regular patient visits.
- Digital rectal examinations.
- Prostate-specific antigen (PSA) testing.
- Transrectal ultrasound.
- Transrectal needle biopsies.

Patient selection, testing intervals, and specific tests, as well as criteria for intervention, are arbitrary and not established in controlled trials.

In the United States, as in other settings with widespread PSA screening, the results of conservative management of localized prostate cancer are particularly favorable. In the aggregate, men managed by watchful waiting or active surveillance (using various criteria, depending upon the study) have had very favorable prostate-cancer-specific mortalities ranging from about 2% to 10%. Many men with screen-detected prostate cancer are, therefore, candidates for active surveillance, with definitive therapy reserved for signs of tumor progression.

Evidence (watchful waiting or active surveillance):

1. A population-based study with 15 years of follow-up (mean observation time of 12.5 years) has shown excellent survival without any treatment in patients with well-differentiated tumors or moderately well-differentiated tumors clinically confined to the prostate, irrespective of age.[8]
   - Tumor was not detected in any of these men by PSA screening, since PSA was not available at the time.
   - The patient cohort was followed for a mean of 21 years after initial diagnosis.[9] The risk of prostate cancer progression and prostate cancer death persisted throughout the follow-up period.
   - By the end of follow-up, 91% of the cohort had died; 16% had died of prostate cancer.

2. A second, smaller population-based study of 94 patients with clinically localized prostate cancer managed by a watch-and-wait strategy had very similar results at 4 to 9 years of follow-up.[10]

3. In a selected series of 50 Jewett stage C patients, 48 of whom had well-differentiated tumors or moderately well-differentiated tumors, the prostate cancer-specific survival rate at 5 years was 88% and, at 9 years, the rate was 70%.[11]

4. In a population-based Surveillance, Epidemiology and End Results (SEER) Medicare-linked database, 14,516 men with localized prostate cancer (T1 or T2 cancer) diagnosed from 1992 to 2002 were followed on conservative management (no surgery or radiation for at least 6 months) for a median of 8.3 years. The median age at diagnosis was 78 years.[12][Levels of evidence: 3iA, 3iB]
   - At 10 years, the prostate cancer-specific mortality rates were 8.3% for men with well-differentiated tumors, 9.1% for men with moderately well-differentiated tumors, and 25.6% for men with poorly differentiated tumors.
   - Corresponding risks of dying of other causes were 59.8%, 57.2%, and 56.6%, respectively.

5. Another population-based observational study of men with clinically localized prostate cancer diagnosed in the PSA-screening era has also been reported, with a median follow-up of 8.2 years.[13] A nationwide Swedish cohort of 6,849 men aged 70 years or younger with T1 or T2 prostate cancer, Gleason scores of 7 or lower, and serum PSA levels of lower than 20 ng/ml was followed after an initial strategy of surveillance (n = 2,021), radical prostatectomy (n = 3,399), or radiation therapy (n = 1,429).[13][Levels of evidence: 3iA, 3iB]
   - The cumulative risk of prostate cancer-specific death at 10 years was 3.6% in the initial surveillance group and 2.7% in the curative intent groups (i.e., 2.4% in the prostatectomy group and 3.3% in the radiation therapy group).
   - The 10-year risk of dying from causes other than prostate cancer was 19.2% in the surveillance group.
versus 10.2% in the curative intent group, showing evidence of selection of patients who were not as healthy for surveillance on average.

- Tumor pathologic characteristics of 222 men in that cohort who followed an initial strategy of surveillance but underwent deferred prostatectomy at a median of 19.2 months (10th–90th percentile, 9.2–45.5 months) were compared with those who underwent immediate prostatectomy. There were no differences between the groups in extraprostatic extension or tumor margin positivity. Although the Gleason scores at radical prostatectomy were higher in the surveillance group than in the immediate prostatectomy group, this occurred concurrently with a national training effort in prostate tumor pathology evaluation that led to the upgrading of tumor specimens. Therefore, the investigators concluded that the delay in prostatectomy in the surveillance group artifactually led to the assignment of higher tumor grades.

6. In a prospective single-center study, 993 men with favorable or intermediate-risk prostate cancer (Gleason score ≤6, PSA ≤20; or Gleason score ≤ [3 + 4] with life expectancy <10 years) were followed with active surveillance, and definitive therapy was reserved for patients with evidence of clinical progression. Level of evidence: 3iiD) Prostate biopsies were performed a year after diagnosis, and then every 3 to 4 years, to check for progression.

- With a median follow-up of 6.4 years (range 0.2–19.8 years), 149 patients (15%) had died of any cause, and 15 of those patients died of prostate cancer (1.5%).
- Prostate cancer-specific survival rates were 98.1% at 10 years and 94.3% at 15 years.
- The proportions of men who remained untreated were 75.7% at 5 years, 63.5% at 10 years, and 55.0% at 15 years.

7. A retrospective analysis of outcomes of men with prostate cancer demonstrated a 10-year disease-specific survival rate of 94% for expectant management for Gleason score 2 to 4 tumors and 75% for Gleason score 5 to 7 tumors; this is similar to a previous study using the SEER database with survival rates of 93% and 77%, respectively.

8. In a retrospective analysis from the European Randomized Study of Screening for Prostate Cancer (ERSPC), 616 men (mean age of 66.3 years) diagnosed with prostate cancer in the screening arm met criteria for active surveillance that included PSA (≤10 ng/ml). PSA density (<0.2 ng/ml), tumor stage T1c/T2, Gleason score (≤3 + 3 = 6), or two or more positive biopsy cores. Level of evidence: 3iiB

- With a median follow-up of 3.91 years, the 10-year prostate cancer-specific survival rate was 100%. By 7.75 years, 50% of men had received active treatment (but 55.8% of these men received treatment despite continued favorable PSA and PSA-doubling time). The overall survival (OS) rate at 10 years was 77%.

(Refer to the Stage II Prostate Cancer Treatment section of this summary for more information.)

**Radical Prostatectomy**

A radical prostatectomy is usually reserved for patients who:

- Are in good health and elect surgical intervention.
- Have tumor confined to the prostate gland (stage I and stage II).

Prostatectomy can be performed by the perineal or retropubic approach. The perineal approach requires a separate incision for lymph node dissection. Laparoscopic lymphadenectomy is technically possible and accomplished with much less patient morbidity. For small, well-differentiated nodules, the incidence of positive pelvic nodes is less than 20%, and pelvic node dissection may be omitted. With larger, less-differentiated tumors, a pelvic lymph node dissection is more important. The value of pelvic node dissection (i.e., open surgical or laparoscopic) in these cases is not therapeutic but spares patients with positive nodes the morbidity of prostatectomy. Radical prostatectomy is not usually performed if frozen section evaluation of pelvic nodes reveals metastases; such patients should be considered for entry into existing clinical trials or receive radiation therapy to control local symptoms.

The role of preoperative (neoadjuvant) hormonal therapy is not established.
After radical prostatectomy, pathologic evaluation stratifies tumor extent into the following classes:

- Margin-positive disease—The incidence of disease recurrence increases when the tumor margins are positive. [8,11,25] Results of the outcome of patients with positive surgical margins have not been systematically reported.

- Specimen-confined disease—The incidence of disease recurrence increases when the tumor is not specimen-confined (extracapsular).[8,11]

- Organ-confined disease—Patients with extraprostatic disease (not organ-confined) are suitable candidates for clinical trials of which the Radiation Therapy Oncology Group's (RTOG) RTOG-9601 (NCT00002874) trial, was an example. These trials have included evaluation of postoperative radiation delivery, cytotoxic agents, and hormonal treatment using luteinizing hormone-releasing hormone (LH-RH) agonists and/or antiandrogens.

**Radical prostatectomy compared with other treatment options**

In 1993, a structured literature review of 144 papers was done in an attempt to compare the three primary treatment strategies for clinically localized prostate cancer:[26]

1. Radical prostatectomy.
2. Definitive radiation therapy.
3. Observation (watchful waiting or active surveillance).

The authors concluded that poor reporting and selection factors within all series precluded a valid comparison of efficacy for the three management strategies.

In a literature review of case series of patients with palpable, clinically localized disease, the authors found that 10-year prostate cancer-specific survival rates were best in radical prostatectomy series (about 93%), worst in radiation therapy series (about 75%), and intermediate with deferred treatment (about 85%).[27] Because it is highly unlikely that radiation therapy would worsen disease-specific survival, the most likely explanation is that selection factors affect choice of treatment. Such selection factors make comparisons of therapeutic strategies imprecise.[28]

Radical prostatectomy has been compared with watchful waiting or active surveillance in men with early-stage disease (i.e., clinical stages T1b, T1c, or T2) in randomized trials, with conflicting results. The difference in results may be the result of differences in how the men were diagnosed with prostate cancer.

Evidence (radical prostatectomy vs. watchful waiting or active surveillance):

1. In a randomized clinical trial performed in Sweden in the pre-PSA screening era, 695 men with prostate cancer were randomly assigned to radical prostatectomy versus watchful waiting. Only about 5% of the men in the trial had been diagnosed by PSA screening. Therefore, the men had more extensive local disease than is typically the case in men diagnosed with prostate cancer in the United States.[29-31]
   - The cumulative overall mortality at 18 years was 56.1% in the radical prostatectomy arm and 68.9% in the watchful waiting study arm (absolute difference, 12.7%; 95% confidence interval [CI], 5.1–20.3 percentage points; relative risk [RR] of death, 0.71; 95% CI, 0.59–0.86).[31][Level of evidence: 1iiA]
   - The cumulative incidence of prostate cancer deaths at 18 years was 17.7% versus 28.7% (absolute difference, 11.0%; 95% CI, 4.5–17.5 percentage points; RR from prostate cancer, 0.56; 95% CI, 0.41–0.77).[31]
   - In a post-hoc–subset analysis, the improvement in overall and prostate cancer-specific mortality associated with radical prostatectomy was restricted to men younger than 65 years.

2. The Prostate Intervention Versus Observation Trial (PIVOT-1 or VA-CSP-407 [NCT00002606]) is the only published randomized trial conducted in the PSA screening era that directly compared radical prostatectomy with watchful waiting. From November 1994 through January 2002, 731 men aged 75 years or younger with localized prostate cancer (stage T1–2, NX, M0, with a blood PSA <50 ng/ml) and a life expectancy of at least 10 years were randomly assigned to radical prostatectomy versus watchful waiting.[3,32][Levels of evidence 1iiA,
About 50% of the men had nonpalpable, screen-detected disease.

After a median follow-up of 10 years (range up to about 15 years), the all-cause mortality was 47.0% versus 49.9% in the prostatectomy and watchful-waiting study arms, respectively, a difference that was not statistically significant (hazard ratio [HR], 0.88; 95% CI, 0.71–1.08; \( P = .22 \)). Prostate cancer-specific mortality was 5.8% versus 8.4%, and it also was not statistically significant (HR, 0.63; 95% CI, 0.36–1.09; \( P = .09 \)).

Subgroup analyses showed a statistically significant reduction in overall mortality in the group of men with a baseline PSA greater than 10 ng/ml (61 of 126 men vs. 77 of 125 men; HR, 0.67) but no difference in men with a PSA of 10 ng/ml or less (110 of 238 men vs. 101 of 241 men; HR, 1.03; \( P \) value for interaction = .04). Because the test for interaction was not adjusted for the numerous subgroup comparisons, it should be interpreted with caution.

Although there was a trend favoring prostatectomy, for prostate cancer-specific mortality, in men with a PSA greater than 10 ng/ml, the numbers were very small (7 of 126 men vs. 16 of 125 men for a PSA >10 ng/ml; 14 of 238 men vs. 15 of 241 men with lower PSA levels), and the interaction with the PSA level was not statistically significant (\( P = .11 \)). There were no statistically significant differences in efficacy associated with prostatectomy by age (<65 years vs. ≥65 years), Gleason score, Charlson comorbidity status, race, or performance score.

Complications of radical prostatectomy

Complications of radical prostatectomy include the following:

- Morbidity and mortality associated with general anesthesia and a major surgical procedure.[33-35]
- Urinary incontinence and impotence.[36-43]
- Penile shortening.[44-46]
- Inguinal hernia.[47-51]
- Fecal incontinence.[52]

Morbidity and mortality associated with radical prostatectomy

An analysis of Medicare records on 101,604 radical prostatectomies performed from 1991 to 1994 showed the following:[33]

- A 30-day operative mortality rate of 0.5%.
- A rehospitalization rate of 4.5%.
- A major complication rate of 28.6%.

Over the study period, these rates decreased by 30%, 8%, and 12%, respectively.[33]

Prostatectomies done at hospitals where fewer of the procedures were performed than those done at hospitals where more were performed were associated with the following:[34,35]

- Higher rates of 30-day postoperative mortality.
- Major acute surgical complications.
- Longer hospital stays.
- Higher rates of rehospitalization.

Operative morbidity and mortality rates increase with age. Comorbidity, especially underlying cardiovascular disease and a history of stroke, accounts for a portion of the age-related increase in 30-day mortality.
In a cohort of all men with prostate cancer who underwent radical prostatectomy from 1990 to 1999 in Ontario, 75-year-old men with no comorbidities had a predicted 30-day mortality of 0.74%. Thirty-day surgical complication rates also depended more on comorbidity than age (i.e., about 5% vs. 40% for men with 0 vs. ≥4 underlying comorbid conditions, respectively).[35]

**Urinary incontinence and impotence**

Urinary incontinence and impotence are complications that can result from radical prostatectomy and have been studied in multiple studies.

Evidence (urinary incontinence and impotence after radical prostatectomy):

1. A large case series of men undergoing the anatomic (nerve-sparing) technique of radical prostatectomy reported the following:[37]
   - Approximately 6% of the men required the use of pads for urinary incontinence, but an unknown additional proportion of men had occasional urinary dribbling.
   - About 40% to 65% of the men who were sexually potent before surgery retained potency adequate for vaginal penetration and sexual intercourse. Preservation of potency with this technique is dependent on tumor stage and patient age, but the operation probably induces at least a partial deficit in nearly all patients.

2. A national survey of Medicare patients who underwent radical prostatectomy in 1988 to 1990 reported more morbidity than in the case series reported above.[38]
   - More than 30% of the men reported the need for pads or clamps for urinary wetness, and 63% of all patients reported a current problem with wetness.
   - About 60% of the men reported having no erections since surgery; about 90% of the men had no erections sufficient for intercourse during the month before the survey.
   - About 28% of the patients reported follow-up treatment of cancer with radiation therapy and/or hormonal therapy within 4 years after their prostatectomy.

3. A population-based longitudinal cohort (Prostate Cancer Outcomes Study) of 901 men aged 55 to 74 years who had recently undergone radical prostatectomy for prostate cancer reported the following:[39]
   - 15.4% of the men had either frequent urinary incontinence or no urinary control at 5 years after surgery.
   - 20.4% of those studied wore pads to stay dry.
   - 79.3% of men reported an inability to have an erection sufficient for intercourse.

4. A cross-sectional survey of prostate cancer patients who were treated with radical prostatectomy, radiation therapy, or watchful waiting and active surveillance in a managed care setting showed substantial sexual and urinary dysfunction in the prostatectomy group.[40]
   - Results reported by the patients were consistent with those from the national Medicare survey.
   - In addition, although statistical power was limited, differences in sexual and urinary dysfunction between men who had undergone either nerve-sparing or standard radical prostatectomy were not statistically significant. This issue requires more study.

5. Case series of 93, 459, and 89 men who had undergone radical prostatectomy by experienced surgeons showed rates of impotence as high as those in the national Medicare survey when men were carefully questioned about sexual potency, although the men in these case series were on average younger than those in the Medicare survey.[41-43] One of the case series used the same questionnaire as that used in the Medicare survey.[41] The urinary incontinence rate in that series was also similar to that in the Medicare survey.

Differences are often reported between population-based surveys and case series from individual centers. Reasons could include the following:
• Age differences among the populations.
• Surgical expertise at the major reporting centers.
• Patient selection factors.
• Publication bias of favorable series.
• Different methods of collecting information from patients.

**Penile shortening**

Case series of men who have undergone radical prostatectomy have shown shortening of penile length (by an average of 1–2 cm).[44-46] The functional consequence of the shortening is not well studied, but it is noticeable to some men.

In a registry of men with rising PSA after initial treatment of clinically localized prostate cancer, 19 of 510 men (3.7%) who had undergone radical prostatectomy complained of reduced penile size.[53] However, the data were based upon physician reporting of patients' complaints rather than direct patient questioning or before-and-after measurement of penile length. Also, the study sample was restricted to patients with known or suspected tumor recurrence, making generalization difficult.

**Inguinal hernia**

Inguinal hernia has been reported as a complication of radical prostatectomy.

Evidence (inguinal hernia after radical prostatectomy):

1. Retrospective cohort studies and case series have shown an increased incidence of inguinal hernia, in the range of 7% to 21%, in men undergoing radical prostatectomy, with rates peaking within 2 years of surgery.[47-51]

2. Observational studies suggest that the rates are higher than in comparable men who have undergone prostate biopsy alone, transurethral resections, and simple open prostatectomy for benign disease;[47,48] or in men with prostate cancer who have undergone pelvic lymph node dissection alone or radiation therapy.[47,49,50]

Although the observations of increased rates of inguinal hernia after radical prostatectomy are consistent, it is conceivable that men with prostate cancer who are being followed carefully by urologists could have higher detection rates of hernia as a result of frequent examinations or diagnostic imaging (i.e., detection bias). Men should be made aware of this potential complication of prostatectomy.

**Fecal incontinence**

Radical prostatectomy may cause fecal incontinence, and the incidence may vary with surgical method.[52]

Evidence (fecal incontinence after radical prostatectomy):

1. In a national survey sample of 907 men who had undergone radical prostatectomy at least 1 year before the survey, 32% of the men who had undergone perineal (nerve-sparing) radical prostatectomy and 17% of the men who had undergone retropubic radical prostatectomy reported accidents of fecal leakage. Ten percent of the respondents reported moderate amounts of fecal leakage, and 4% of the respondents reported large amounts of fecal leakage. Fewer than 15% of men with fecal incontinence had reported it to a physician or health care provider.[52]

**Radiation Therapy and Radiopharmaceutical Therapy**

**External-beam radiation therapy (EBRT)**

Candidates for definitive radiation therapy must have a confirmed pathologic diagnosis of cancer that is clinically confined to the prostate and/or surrounding tissues (stage I, stage II, and stage III). Staging laparotomy and lymph node dissection are not required.

Radiation therapy may be a good option for patients who are considered poor medical candidates for radical prostatectomy. These patients can be treated with an acceptably low complication rate if care is given to the delivery...
Long-term results with radiation therapy are dependent on stage and are associated with dosimetry of the radiation.

Evidence (EBRT):

1. A retrospective review of 999 patients treated with megavoltage radiation therapy showed that cause-specific survival rates at 10 years varied substantially by T stage: T1 (79%), T2 (66%), T3 (55%), and T4 (22%). An initial serum PSA level higher than 15 ng/ml is a predictor of probable failure with conventional radiation therapy.

2. Several randomized studies have demonstrated an improvement in freedom from biochemical (PSA based) recurrence with higher doses of radiation therapy (74–79 Gy) as compared with lower doses (64–70 Gy). None of the studies demonstrated a cause-specific survival benefit to higher doses. For example, in the MRC-RT01 [NCT00003290] study that was powered to detect differences in both biochemical progression-free survival (PFS) and a 15% difference in OS, 843 men with stage T1b through T3a, N0, M0 prostate cancer were randomly assigned to receive 64 Gy in 32 fractions versus 74 Gy in 37 fractions by conformal delivery. Men in both study groups received neoadjuvant LH-RH agonist injections every 4 weeks for 3 to 6 months before the start of radiation therapy and throughout the radiation course. After a median follow-up of 10 years, despite a statistically significant improvement in biochemical PFS with the higher dose of radiation, the 10-year OS was the same in both groups: 71% (HR, 0.99; 95% CI, 0.77–1.28; \(P = .96\)). Likewise, there were no differences in prostate cancer-specific survival.

Prophylactic radiation therapy to clinically or pathologically uninvolved pelvic lymph nodes does not appear to improve OS or prostate cancer-specific survival as was seen in the RTOG-7706 trial, for example.

Evidence (conventional vs. hypofractionated EBRT):

On the basis of limited data from randomized trials, the more convenient schedules of hypofractionated radiation therapy (using fewer fractions at higher doses per fraction) appear to yield similar outcomes to conventional schedules of radiation, at least with respect to the intermediate outcome of DFS—a low level of evidence not known to translate into health outcomes—but potentially offering more convenient schedules of treatment.

Conventional versus hypofractionated EBRT

Evidence (conventional vs. hypofractionated EBRT):

1. In a small, randomized trial, primarily from one treatment center, conventional hypofractionation was not found to be superior to conventional fractionation. In the trial, 303 assessable men were randomly assigned to receive intensity-modulated radiation therapy (IMRT) for a total of 76 Gy in 38 fractions at 2.0 Gy per fraction (conventional IMRT [CIMRT]) versus IMRT for a total of 70.2 Gy in 26 fractions at 2.7 Gy per fraction (hypofractionated IMRT [HIMRT]). The primary endpoint was biochemical or clinical disease failure (BCDF). The 5-year BCDF rates in the two arms were 21.4% for the CIMRT arm (95% CI, 14.8%–28.7%) and 23.3% for the HIMRT arm (95% CI, 16.4%–31.0%), \(P = .75\).

2. In the much larger, multicenter Conventional or Hypofractionated High-Dose Intensity Modulated Radiotherapy in Prostate Cancer (CHHiP) trial [NCT00392535], 3,216 men with stages T1b–T3a, N0, M0 cancer and an estimated risk of seminal vesicle involvement of less than 30% were randomly assigned to receive either 74 Gy in 37 fractions (the conventional-fraction arm), 60 Gy in 20 fractions, or 57 Gy in 19 fractions (1:1:1 ratio).
Importantly, the primary efficacy endpoints are pending. However, a quality-of-life (QOL) substudy was conducted with 2,100 participants and showed nearly identical patient-reported outcomes in each of the three arms at 2 years after study entry (median follow-up = 50 months).[63][Level of evidence: 1iiC]

- The primary endpoint reported by the patients was bowel bother. Frequency of moderate bother was 5%, 6%, and 5% in the three study groups. Severe bother was reported in less than 1% of men in each study group.
- Likewise, there were no differences in any of the secondary outcomes, which included overall QOL, overall urinary bother, or overall sexual bother.

3. In another multicenter, randomized trial of Hypofractionated versus Conventionally Fractionated Radiotherapy for Patients with Prostate Cancer (HYPRO study [ISRCTN85138529]), conventional radiation therapy doses (78 Gy in 39 fractions over 8 weeks) were compared with hypofractionated radiation therapy doses (64.6 Gy in 19 fractions over 6.5 weeks) in a noninferiority design for hypofractionation in 820 men with intermediate- or high-risk prostate cancer (stages T1b–T4, NX–0, MX–0).[64] The primary efficacy endpoints are pending.

- With respect to toxicity (key endpoints of genitourinary [GU] or gastrointestinal [GI] grade 2+ toxicities at 3 years), noninferiority for hypofractionated radiation therapy could not be established after a median follow-up of 5 years: cumulative GU toxicity of 41.3% with hypofractionated radiation therapy versus 39% with conventional radiation therapy doses (HR, 1.16; 90% CI, 0.98–1.38); GI toxicity of 21.9% versus 17.7% (HR, 1.19; 90% CI, 0.93–1.52).
- Cumulative GU grade 3+ toxicity was higher in the hypofractionation group: 19.0% versus 12.9% ($P = .02$).
- Stool frequency (≥6 per day) was higher in the hypofractionation group: 7% versus 3% ($P = .034$).

4. The RTOG reported a noninferiority trial of 1,115 men with low-risk prostate cancer (T1b–T2c) who were randomly assigned to receive hypofractionated radiation therapy (70 Gy in 28 fractions over 5.6 weeks) versus conventional radiation therapy doses (73.8 Gy in 41 fractions over 8.2 weeks).[65]

- After a median follow-up of 5.8 years, the hypofractionated radiation therapy arm met the prospective noninferiority criterion with respect to DFS: 86.3% with hypofractionated radiation therapy versus 85.3% with conventional radiation therapy doses (consistent with HR, <1.52; $P < .001$ for the hypothesis of noninferiority).[65][Level of evidence: 1iiDii]
- There were 49 deaths in the hypofractionated radiation therapy arm and 51 deaths in the conventional radiation therapy doses arm (HR for OS, 0.95; conventional radiation therapy doses vs. hypofractionated radiation therapy; 95% CI, 0.64–1.41).
- However, late GI grade 2+ toxicity was worse in the hypofractionated radiation therapy arm: 22.4% versus 14.0% ($P = .002$); there was also a trend toward worse late GU grade 2+ toxicity: 29.7% versus 22.8% ($P = .06$).

**Brachytherapy**

Patients undergoing brachytherapy are often selected for favorable characteristics that include the following:

- Low Gleason score.
- Low PSA level.
- Stage T1 to T2 tumors.

More information and further study are required to better define the effects of modern interstitial brachytherapy on disease control and QOL and to determine the contribution of favorable patient selection to outcomes.[66][Level of evidence: 3iiiDiv]

Information about ongoing clinical trials is available from the NCI website.
**Radiopharmaceutical therapy**

**Alpha emitter radiation**

Radium-223 emits alpha particles (i.e., two protons and two neutrons bound together, identical to a helium nucleus) with a half-life of 11.4 days. It is administered intravenously and selectively taken up by newly formed bone stroma. The high-energy alpha particles have a short range of less than 100 mcM. Radium-223 improved OS in patients with prostate cancer metastatic to bone. In a double-blind, randomized, controlled trial, 921 men with symptomatic castration-resistant prostate cancer, two or more metastases, and no known visceral metastases were randomly assigned in a 2:1 ratio to radium-223 versus placebo. Radium-223 statistically significantly improved OS (median 14.9 months vs. 11.3 months), rate of symptomatic skeletal events (33% vs. 38%), and spinal cord compression (4% vs. 7%).[67,68][Level of evidence: 1iA] With administration at a dose of 50kBq per kg body weight every 4 weeks for six injections, the side effects were similar to those of a placebo.

**Complications of radiation therapy**

Definitive EBRT can result in acute cystitis, proctitis, and enteritis.[18,36,43,69-71] These conditions are generally reversible but may be chronic and rarely require surgical intervention.[71]

A cross-sectional survey of prostate cancer patients who had been treated in a managed care setting by radical prostatectomy, radiation therapy, or watchful waiting and active surveillance showed substantial sexual and urinary dysfunction in the radiation therapy group.[40]

Radiation is also known to be carcinogenic.[72-74] EBRT for prostate cancer is associated with an increased risk of bladder and gastrointestinal cancer. Brachytherapy is associated with an increased risk of bladder cancer.

**Reducing complications**

Potency, in most cases, is preserved with radiation therapy in the short term but appears to diminish over time.[71]

Sildenafil citrate may be effective in the management of sexual dysfunction after radiation therapy in some men.

Evidence (reducing complications):

1. In a completed, randomized, placebo-controlled, crossover design study (RTOG-0215 [NCT00057759]) of 60 men who had undergone radiation therapy for clinically localized prostate cancer, and who reported erectile dysfunction that began after their radiation therapy, 55% reported successful intercourse after sildenafil versus 18% after placebo ($P < .001$).[75][Level of evidence: 1iC]

2. A randomized trial (RTOG-0831 [NCT00931528]) of 121 men with intact erectile function compared daily preventive tadalafil (5 mg orally per day) with placebo for 24 weeks beginning at the start of either EBRT or brachytherapy.[76][Level of evidence: 1iC]
   - There were no statistically significant differences in spontaneous erectile function (the primary endpoint) or any other measures of sexual function.

Morbidity may be reduced with the employment of sophisticated radiation therapy techniques—such as the use of linear accelerators—and careful simulation and treatment planning.[77,78]

Evidence (3-dimensional conformal vs. conventional radiation therapy):

1. The side effects of similar doses of 3-D conformal radiation therapy and conventional radiation therapy (total dose = 60–64 Gy) have been compared in a randomized nonblinded study.[78][Level of evidence: 1iC]
   - No differences were observed in acute morbidity, and late side effects serious enough to require hospitalization were infrequent with both techniques; however, the cumulative incidence of mild or greater proctitis was lower in the conformal radiation arm than in the standard therapy arm (37% vs. 56%; $P = .004$). Urinary symptoms were similar in the two treatment groups, as were local tumor control and OS rates at 5 years of follow-up.

Radiation therapy can be delivered after an extraperitoneal lymph node dissection without an increase in complications.
if careful attention is paid to radiation technique. The treatment field should not include the area that contained the dissected pelvic nodes. Previous TURP is associated with an increased risk of stricture above that seen with radiation therapy alone, but, if radiation therapy is delayed 4 to 6 weeks after the TURP, the risk of stricture is lower.[79-81] Pretreatment TURP to relieve obstructive symptoms has been associated with tumor dissemination; however, multivariable analysis in pathologically staged cases indicates that this may be due to a worse underlying prognosis of the cases that require TURP rather than the result of the procedure itself.[82]

**Comparison of complications from radiation therapy and from radical prostatectomy**

In general, radical prostatectomy is associated with a higher rate of urinary incontinence and early sexual impotence but a lower rate of stool incontinence and rectal injury. However, over time, the differences in sexual impotence diminish because the risk rises with time since radiation.

Evidence (complications of radical prostatectomy vs. radiation therapy):

1. A population-based survey of Medicare recipients who had received radiation therapy as primary treatment for prostate cancer (similar in design to the survey of Medicare patients who underwent radical prostatectomy,[38] described above) has been reported, showing substantial differences in posttreatment morbidity profiles between surgery and radiation therapy.[83]
   - Although the men who had undergone radiation therapy were older at the time of initial therapy, they were less likely to report the need for pads or clamps to control urinary wetness (7% vs. >30%).
   - A larger proportion of patients treated with radiation therapy before surgery reported the ability to have an erection sufficient for intercourse in the month before the survey (men <70 years, 33% who received radiation therapy vs. 11% who underwent surgery alone; men ≥70 years, 27% who received radiation therapy vs. 12% who underwent surgery alone).
   - Men receiving radiation therapy, however, were more likely to report problems with bowel function, especially frequent bowel movements (10% vs. 3%).
   - As in the results of the surgical patient survey, about 24% of patients who received radiation reported additional subsequent treatment for known or suspected cancer persistence or recurrence within 3 years of primary therapy.

2. A prospective, community-based cohort study of men aged 55 to 74 years treated with radical prostatectomy (n = 1,156) or EBRT (n = 435) attempted to compare the acute and chronic complications of the two treatment strategies after adjusting for baseline differences in patient characteristics and underlying health.[84]
   - Regarding acute treatment-related morbidity, radical prostatectomy was associated with higher rates of cardiopulmonary complications (5.5% vs. 1.9%) and the need for treatment of urinary strictures (17.4% vs. 7.2%). Radiation therapy was associated with more acute rectal proctitis (18.7% vs. 1.6%).
   - With regard to chronic treatment-related morbidity, radical prostatectomy was associated with more urinary incontinence (9.6% vs. 3.5%) and impotence (80% vs. 62%). Radiation therapy was associated with slightly greater declines in bowel function.

**Hormonal Therapy and Its Complications**

Several different hormonal approaches are used in the management of various stages of prostate cancer.

These approaches include the following:

- Bilateral orchietomy.
- Estrogen therapy.
- Leuteinizing hormone-releasing hormone (LH-RH) agonist therapy.
- Antiandrogen therapy.
- Androgen deprivation therapy (ADT).
Antiadrenal therapy.
- Ketoconazole.
- Aminoglutethimide.

Bilateral orchiectomy

Benefits of bilateral orchiectomy include the following:[36]

- Ease of the procedure.
- Compliance.
- Immediacy in lowering testosterone levels.
- Low cost relative to the other forms of ADT.

Disadvantages of bilateral orchiectomy include the following:[36,85]

- Psychological effects.
- Loss of libido.
- Less reversible impotence.
- Hot flashes.
- Osteoporosis.[85]

Bilateral orchiectomy has also been associated with an elevated risk of coronary heart disease and myocardial infarction.[86-89]

(Refer to the PDQ summary on Hot Flashes and Night Sweats.)

Estrogen therapy

Estrogens at a dose of 3 mg per day of diethylstilbestrol (DES) will achieve castrate levels of testosterone. Like orchiectomy, estrogens may cause loss of libido and impotence. Estrogens also cause gynecomastia, and prophylactic low-dose radiation therapy to the breasts is given to prevent this complication.

DES is no longer manufactured or marketed in the United States and is seldom used today because of the risk of serious side effects, including myocardial infarction, cerebrovascular accidents, and pulmonary embolism.

LH-RH agonist therapy

LH-RH agonists, such as leuprolide, goserelin, and buserelin lower testosterone to castrate levels. Like orchiectomy and estrogens, LH-RH agonists cause impotence, hot flashes, and loss of libido. Tumor flare reactions may occur transiently but can be prevented by antiandrogens or short-term estrogens at a low dose for several weeks.

There is some evidence that LH-RH agonists are associated with increased risk of cardiovascular morbidity or mortality, although the results are conflicting.[86-90]

Evidence (LH-RH agonists and cardiovascular disease):

1. In a population-based study within the Department of Veterans Affairs' system, LH-RH agonists were associated with an increased risk of diabetes as well as cardiovascular disease, including coronary heart disease, myocardial infarction, sudden death, and stroke.[86-88]

2. A systematic evidence review and meta-analysis of eight trials (4,141 patients) of men with nonmetastatic prostate cancer who were randomly assigned to receive or not to receive LH-RH agonists found no difference in cardiovascular death rates (11.0% vs. 11.2%; RRdeath of 0.93; 95% CI, 0.79–1.10; P = .41).[91] Median follow-up in those studies was 7.6 to 13.2 years. No excess risk of LH-RH agonists was found regardless of
treatment duration or patient age (median age of <70 years or ≥70 years).

**Antiandrogen therapy**

Antiandrogen agents used in the treatment of prostate cancer include flutamide and bicalutamide. The pure antiandrogen, flutamide, may cause diarrhea, breast tenderness, and nausea. Case reports show fatal and nonfatal liver toxic effects.[92]

Bicalutamide may cause nausea, breast tenderness, hot flashes, loss of libido, and impotence.[93] (Refer to the PDQ summaries on Gastrointestinal Complications; Nausea and Vomiting; and Hot Flashes and Night Sweats for more information.)

The steroidal antiandrogen, megestrol acetate, suppresses androgen production incompletely and is generally not used as initial therapy.

Additional studies that evaluate the effects of various hormone therapies on QOL are required.[94]

**ADT**

A national Medicare survey of men who had undergone radical prostatectomy for prostate cancer and either had or had not undergone androgen depletion (either medically or surgically induced) showed a decrease with androgen depletion in all seven health-related, QOL measures, including:[95][Level of evidence: 3iC]

- Concern regarding body image.
- Mental health.
- General health.
- Activity.
- Worries about cancer and dying.
- Energy.

ADT can cause osteoporosis and bone fractures. In a population-based sample of 50,613 Medicare patients aged 66 years or older followed for a median of 5.1 years, men who had been treated with either a gonadotropin-releasing hormone (GnRH) or orchiectomy had a 19.4% bone fracture rate compared with 12.6% in men who had not received hormone deprivation therapy. The effect was similar in men whether or not they had metastatic bone disease.[96]

The use of ADT may be associated with complaints of penile shortening, although the data are very limited.[53] In a registry study of men with rising PSA after initial treatment of clinically localized prostate cancer treated with radiation therapy plus ADT, 6 of 225 men (2.7%) complained of reduced penile size. Of the 213 men treated with radiation therapy but no ADT, none complained of changes in penile size. However, the data were based upon physician reporting of patients' complaints rather than direct patient questioning or before-and-after measurement of penile length. Also, the study sample was restricted to patients with known or suspected tumor recurrence, making generalization difficult.

Placebo-controlled, randomized trials have shown that treatment of bone loss with bisphosphonates decreases the risk of bone fracture in men receiving ADT for prostate cancer (RR, 0.80 in a meta-analysis of 15 trials; 95% CI, 0.69–0.94). In the meta-analysis, zoledronate appeared to have the largest effect.[97]

The use of ADT has also been associated with an increased risk of colorectal cancer.

Evidence (increased risk of colorectal cancer):

1. Using the SEER Medicare database, investigators assessed the risk of subsequent colorectal cancer in 107,859 men aged 67 years and older after an initial diagnosis of prostate cancer.[98]
   - The rates of colorectal cancer per 1,000 person-years were 6.3 (95% CI, 5.3–7.5) in men who had orchiectomy, 4.4 (95% CI, 4.0–4.9) in men treated with GnRH agonists, and 3.7 (95% CI, 3.5–3.9) in men
who had no androgen deprivation.

- In men treated with GnRH agonists, the risk increased with increasing duration of treatment ($P$ for trend = .01).

**Antiadrenal therapy**

Antiadrenal agents used in the treatment of prostate cancer include ketoconazole and aminoglutethimide. Long-term use of ketoconazole can result in impotence, pruritus, nail changes, and adrenal insufficiency. (Refer to the PDQ summary on Pruritus for more information.) Aminoglutethimide commonly causes sedation and skin rashes.

**Treatment Options Under Clinical Evaluation**

**Cryosurgery**

Cryosurgery, or cryotherapy, is under evaluation for the treatment of localized prostate cancer. It is a surgical technique that involves destruction of prostate cancer cells by intermittent freezing of the prostate with cryoprobes, followed by thawing.[99][Level of evidence: iiiC]; [Level of evidence: iii][100,101][Level of evidence: iiiDiv] There is limited evidence regarding its efficacy and safety compared with standard prostatectomy and radiation therapy, and the technique is evolving in an attempt to reduce local toxicity and normal tissue damage. The quality of evidence on efficacy is low, currently limited to case series of relatively small size, short follow-up, and surrogate outcomes of efficacy.[102]

Serious toxic effects associated with cryosurgery include bladder outlet injury, urinary incontinence, sexual impotence, and rectal injury. Impotence is common, ranging from about 47% to 100%.

The frequency of other side effects and the probability of cancer control at 5 years' follow-up have varied among reporting centers, and series are small compared with surgery and radiation therapy.[100,101] Other major complications include urethral sloughing, urinary fistula or stricture, and bladder neck obstruction.[102]

**Proton-beam therapy**

There is interest in the use of proton-beam therapy for the treatment of prostate cancer. Although the dose distribution of this form of charged-particle radiation could theoretically improve the therapeutic ratio of prostate radiation, allowing for an increase in dose to the tumor without a substantial increase in side effects, no randomized controlled trials have been reported that compare its efficacy and toxicity with those of other forms of radiation therapy.

**Neoadjuvant hormonal therapy**

The role of neoadjuvant hormonal therapy is not established.[23,24]

**Bicalutamide**

Bicalutamide has not been shown to improve OS in patients with localized or locally advanced prostate cancer.

Evidence (bicalutamide):

1. The Early Prostate Cancer program is a large, randomized, placebo-controlled, international trial that compared bicalutamide (150 mg orally per day) plus standard care (radical prostatectomy, radiation therapy, or watchful waiting, depending on local custom) with standard care alone for men with nonmetastatic localized or locally advanced prostate cancer (T1–2, N0, and NX; T3–4, any N; or any T, N+). Less than 2% of the 8,113 men had known nodal disease.[103][Level of evidence: iIA]

   - At a median follow-up of 7.4 years, there was no difference in OS between the bicalutamide and placebo groups (about 76% in both arms [HR, 0.99; CI, 95%, 0.91–1.09; $P = .89$]).

Information about ongoing clinical trials is available from the NCI website.

**References**
23. Witjes WP, Schulman CC, Debruyne FM: Preliminary results of a prospective randomized study comparing radical prostatectomy versus radical prostatectomy associated with neoadjuvant hormonal combination therapy in T2-3 N0 M0 prostate carcinoma. The European Study Group on Neoadjuvant Treatment of Prostate Cancer.


Stage I Prostate Cancer Treatment

Overview

Stage I prostate cancer is defined by the American Joint Committee on Cancer's TNM classification system:[1]

- T1a–c, N0, M0, prostate-specific antigen (PSA) <10 ng/ml, Gleason ≤6.
T2a, N0, M0, PSA <10 ng/ml, Gleason ≤6.

T1–2a, N0, M0, PSA X, Gleason X.

The frequency of clinically silent, nonmetastatic prostate cancer that can be found at autopsy greatly increases with age and may be as high as 50% to 60% in men aged 90 years and older. Undoubtedly, the incidental discovery of these occult cancers at prostatic surgery performed for other reasons accounts for the similar survival of men with stage I prostate cancer, compared with the normal male population, adjusted for age.

Many stage I cancers are well differentiated and only focally involve the gland (T1a, N0, M0); most require no treatment other than careful follow-up.[2]

In younger patients (aged 50–60 years) whose expected survival is long, treatment should be considered.[3] Radical prostatectomy, external-beam radiation therapy (EBRT), interstitial implantation of radioisotopes, and watchful waiting and active surveillance yield apparently similar survival rates in noncontrolled, selected series. The decision to treat should be made in the context of the patient’s age, associated medical illnesses, and personal desires.[3]

**Standard Treatment Options for Stage I Prostate Cancer**

Standard treatment options for stage I prostate cancer include the following:

1. Watchful waiting or active surveillance.
2. Radical prostatectomy.
3. External-beam radiation therapy (EBRT).
4. Interstitial implantation of radioisotopes.

**Watchful waiting or active surveillance**

Asymptomatic patients of advanced age or with concomitant illness may warrant consideration of careful observation without immediate active treatment.[4-6] Watch and wait, observation, expectant management, and active surveillance are terms indicating a strategy that does not employ immediate therapy with curative intent. (Refer to the Watchful Waiting or Active Surveillance section in the Treatment Option Overview for Prostate Cancer section of this summary for more information.)

Evidence (observation with delayed hormonal therapy):

1. In a retrospective pooled analysis, 828 men with clinically localized prostate cancer were managed by initial conservative therapy with subsequent hormonal therapy given at the time of symptomatic disease progression.
   - This study showed that the patients with grade 1 or grade 2 tumors experienced a disease-specific survival of 87% at 10 years and that their overall survival (OS) closely approximated the expected survival among men of similar ages in the general population.[4]

**Radical prostatectomy**

Radical prostatectomy, usually with pelvic lymphadenectomy (with or without the nerve-sparing technique designed to preserve potency) is the most commonly applied therapy with curative intent.[7-9] Radical prostatectomy may be difficult after a transurethral resection of the prostate (TURP).

Because about 40% to 50% of men with clinically organ-confined disease are found to have pathologic extension beyond the prostate capsule or surgical margins, the role of postprostatectomy adjuvant radiation therapy has been studied.

Consideration may also be given to postoperative radiation therapy (PORT) for patients who are found to have seminal vesicle invasion by tumor at the time of prostatectomy or who have a detectable level of PSA more than 3 weeks after surgery.[10-12] Because duration of follow-up in available studies is still relatively short, the value of PORT is yet to be determined; however, PORT does reduce local recurrence.[10] Careful treatment planning is necessary to avoid morbidity.
Evidence (radical prostatectomy followed by radiation therapy):

1. In a randomized trial of 425 men with pathologic T3, N0, and M0 disease, postsurgical EBRT (60–64 Gy to the prostatic fossa over 30–32 fractions) was compared with observation.[11][Level of evidence: 1iiA]

   - The primary endpoint, metastasis-free survival, could be affected by serial PSA monitoring and resulting metastatic work-up for PSA increase. This could have biased the primary endpoint in favor of radiation therapy, which was associated with a lower rate of PSA rise. Nevertheless, metastasis-free survival was not statistically different between the two study arms ($P = .06$). After a median follow-up of about 10.6 years, the overall median survival was 14.7 years in the radiation therapy group versus 13.8 years in the observation group ($P = .16$).

   - Although the OS rates were not statistically different, complication rates were substantially higher in the radiation therapy group: overall complications were 23.8% versus 11.9%, rectal complications were 3.3% versus 0%, and urethral stricture was 17.8% versus 9.5%.

   - After a median follow-up of about 12.5 years, however, OS was better in the radiation therapy arm; hazard ratio (HR) of death of 0.72 (95% confidence interval [CI], 0.55–0.96; $P = .023$). The 10-year estimated survival rates were 74% in the radiation therapy arm and 66% in the control arm. The 10-year estimated metastasis-free survivals were 73% and 65% ($P = .016$).[12][Level of evidence: 1iiA]

2. Another randomized trial came to a different conclusion with respect to the effect of postoperative radiation therapy on OS.[13][Level of evidence: 1iiA]. In the European Organization for Research and Treatment of Cancer (EORTC) trial (EORTC-22911 [NCT00002511]), 1,005 men aged 75 years and younger with clinical T0 to T3 prostate cancer were randomly assigned after prostatectomy to receive postoperative radiation (60 Gy) or observation, with subsequent therapy delayed until the occurrence of either biochemical or clinical relapse. The recommended treatment for local recurrence was radiation.

   - With a median follow-up of 10.6 years (up to 16.6 years), the biochemical progression-free survival (PFS) rates were higher in the observation study arm (60.6% vs. 41.1%; HR, 0.49; 95% CI, 0.41–0.59; $P < .0001$). Locoregional relapse rates were 8.4% versus 17.3% in favor of immediate radiation (HR, 0.45; 95% CI, 0.32–0.68; $P < .0001$).

   - However, the large differences in biochemical relapse-free survival and local recurrence did not translate into an advantage in either distant metastasis (11.0% vs. 11.3%; HR, 0.99; 95% CI, 0.67–1.44; $P = .94$) or in OS (76.9% with immediate radiation vs. 80.7% with observation; HR, 1.18; 95% CI, 0.91–1.53; $P = .2$). Nor was there a difference in prostate cancer-specific mortality (3.9% vs. 5.2%; HR, 0.78; 95% CI, 0.46–1.33; $P = .34$).

   - The 10-year cumulative risk of severe (grade 3) late toxicity in the immediate radiation study group was 5.3% versus 2.5% in the observation group ($P = .052$). Late adverse effects of any grade were also higher in the immediate radiation group (70.8% vs. 59.7%; $P = .001$).

Radical prostatectomy has been compared with watchful waiting or active surveillance. (Refer to the Radical prostatectomy compared with other treatment options section in the Treatment Option Overview for Prostate Cancer section of this summary for more information about radical prostatectomy compared with watchful waiting or active surveillance.)

Evidence (radical prostatectomy compared with watchful waiting):

1. The Prostate Intervention Versus Observation Trial (PIVOT-1 or VA-CSP-407 [NCT00002606]) is the only published randomized trial conducted in the PSA screening era that directly compared radical prostatectomy with watchful waiting. From November 1994 through January 2002, 731 men aged 75 years or younger with localized prostate cancer (stage T1–2, NX, M0, with a blood PSA <50 ng/ml) and a life expectancy of at least 10 years were randomly assigned to radical prostatectomy versus watchful waiting.[14,15][Levels of evidence 1iiA, 1iiB]

   - About 50% of the men had nonpalpable, screen-detected disease.
After a median follow-up of 10 years (range up to about 15 years), the all-cause mortality was 47.0% versus 49.9% in the prostatectomy and watchful-waiting study arms, respectively, a difference that was not statistically significant (HR, 0.88; 95% CI, 0.71–1.08; \( P = .22 \)). Prostate cancer-specific mortality was 5.8% versus 8.4%, and it also was not statistically significant (HR, 0.63; 95% CI, 0.36–1.09; \( P = .09 \)).

Subgroup analyses showed a statistically significant reduction in overall mortality in the group of men with a baseline PSA greater than 10 ng/ml (61 of 126 men vs. 77 of 125 men; HR, 0.67) but no difference in men with a PSA of 10 ng/ml or less (110 of 238 men vs. 101 of 241 men; HR, 1.03; \( P \) for interaction = .04). Because the test for interaction was not adjusted for the numerous subgroup comparisons, it should be interpreted with caution.

Although there was a trend favoring prostatectomy, for prostate cancer-specific mortality, in men with a PSA greater than 10 ng/ml, the numbers were very small (7 of 126 men vs. 16 of 125 men for a PSA >10 ng/ml; 14 of 238 men vs. 15 of 241 men with lower PSA levels), and the interaction with the PSA level was not statistically significant (\( P = .11 \)). There were no statistically significant differences in efficacy associated with prostatectomy by age (<65 years vs. \( \geq \)65 years), Gleason score, Charlson comorbidity status, race, or performance score.

External-beam radiation therapy (EBRT)

EBRT is another treatment option used with curative intent.[16-20] Definitive radiation therapy should be delayed 4 to 6 weeks after TURP to reduce the incidence of stricture.[21] Adjuvant hormonal therapy should be considered for patients with bulky T2b to T2c tumors.[22,23]

Evidence (EBRT with or without adjuvant hormonal therapy):

1. Radiation Therapy Oncology Group's (RTOG) trial 7706 (RTOG-7706).[24][Level of evidence: 1iiA]
   - Prophylactic radiation therapy to clinically or pathologically uninvolved pelvic lymph nodes does not appear to improve OS or prostate cancer-specific survival.

2. RTOG-9413 (RTOG-9413 [NCT00769548]) trial.[25]; [26][Level of evidence: 1iiDiii]
   - Although RTOG-9413 showed increased PFS at 4 years for patients who had a 15% estimated risk of lymph node involvement and received whole-pelvic radiation therapy compared with prostate-only radiation therapy, OS and PSA failure rates were not significantly different.

3. In a randomized trial, 875 men with locally advanced nonmetastatic prostate cancer (T1b–T2 moderately or poorly differentiated tumors; T3 tumors of any grade) were randomly assigned to receive 3 months of a luteinizing hormone-releasing hormone agonist plus long-term flutamide (250 mg by mouth three times a day) with or without EBRT.[23][Level of evidence: 1iiA]
   - Nineteen percent of the men had tumor stage T2, and 78% of the men had T3. At 10 years, both overall mortality (29.6% vs. 39.4%; 95% CI for the difference, 0.8%–18.8%) and the prostate cancer-specific mortality (11.9% vs. 23.9%; 95% CI for the difference, 4.9%–19.1%) favored combined hormonal and radiation therapy.
   - Although flutamide might not be considered a standard hormonal monotherapy in the setting of T2 or T3 tumors, it is interesting to see that radiation therapy provided a disease-free survival or tumor-specific survival advantage even though this monotherapy was applied. This analysis rests on the assumption that flutamide does not shorten life expectancy and cancer-specific survival. Radiation therapy was not delivered by current standards of dose and technique.

Interstitial implantation of radioisotopes

Interstitial implantation of radioisotopes (i.e., iodine 125 \(^{125}\)I, palladium, and iridium) done through a transperineal technique with either ultrasound or computed-tomography guidance, is being used in patients with T1 or T2a tumors. Short-term results in these patients are similar to those for radical prostatectomy or EBRT.[27,28]; [29][Level of evidence: 3iiiDiv]
Factors for consideration in the use of interstitial implants include the following:

- The implant is performed as outpatient surgery.
- The rate of maintenance of sexual potency with interstitial implants has been reported to be 86% to 92%.\cite{27,29} In contrast, rates of maintenance of sexual potency with radical prostatectomy were 10% to 40% and 40% to 60% with EBRT.
- Typical side effects from interstitial implants that subside with time include urinary tract frequency, urgency, and less commonly, urinary retention.
- Rectal ulceration may also be seen. In one series, a 10% 2-year actuarial genitourinary grade 2 complication rate and a 12% risk of rectal ulceration were seen. This risk decreased with increased operator experience and modification of the implant technique.\cite{27}

Long-term follow-up of these patients is necessary to assess treatment efficacy and side effects.

Retropubic freehand implantation with $^{125}$I has been associated with an increased local failure and complication rate \cite{30,31} and is now rarely done.

**Treatment Options Under Clinical Evaluation for Stage I Prostate Cancer**

Treatment options under clinical evaluation include the following:

1. High-intensity focused ultrasound therapy.\cite{32-35}

**Current Clinical Trials**

Check the list of NCI-supported cancer clinical trials that are now accepting patients with stage I prostate cancer. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.

**References**


Stage II Prostate Cancer Treatment

Overview
Stage II prostate cancer is defined by the American Joint Committee on Cancer's TNM classification system:[1]

Stage IIA
1. T1a–c, N0, M0, prostate-specific antigen (PSA) <20 ng/ml, Gleason 7.
2. T1a–c, N0, M0, PSA ≥10 <20 ng/ml, Gleason ≤6.
3. T2a, N0, M0, PSA ≥10 <20 ng/ml, Gleason ≤6.
4. T2a, N0, M0, PSA <20 ng/ml, Gleason 7.
5. T2b, N0, M0, PSA <20 ng/ml, Gleason ≤7.
6. T2b, N0, M0, PSA X, Gleason X.

Stage IIB
1. T2c, N0, M0, any PSA, any Gleason.
2. T1–2, N0, M0, PSA ≥20 ng/ml, any Gleason.
3. T1–2, N0, M0, any PSA, Gleason ≥8.

Radical prostatectomy, external-beam radiation therapy (EBRT), and interstitial implantation of radioisotopes are each employed in the treatment of stage II prostate cancer with apparently similar therapeutic effects. Radical prostatectomy and radiation therapy yield apparently similar survival rates with as many as 10 years of follow-up. For well-selected patients, radical prostatectomy is associated with a 15-year survival comparable with an age-matched population without prostate cancer.[2] Unfortunately, randomized comparative trials of these treatment methods with prolonged follow-up are lacking.

Patients with a small, palpable cancer (T2a, N0, and M0) fare better than patients in whom the disease involves both sides of the gland (T2c, N0, and M0). Patients proven free of node metastases by pelvic lymphadenectomy fare better than patients in whom this staging procedure is not performed; however, this is the result of selection of patients who have a more favorable prognosis.

Side effects of the various forms of therapy—including impotence, incontinence, and bowel injury—should be considered in determining the type of treatment to employ.

Prostate-specific antigen (PSA) changes as markers of tumor progression

Often, changes in PSA are thought to be markers of tumor progression. Even though a tumor marker or characteristic may be consistently associated with a high risk of prostate cancer progression or death, it may be a very poor predictor of very limited utility in making therapeutic decisions.

Baseline PSA and rate of PSA change were associated with subsequent metastasis or prostate cancer death in a cohort of 267 men with clinically localized prostate cancer who were managed by watchful waiting or active surveillance in the control arm of a randomized trial comparing radical prostatectomy with watchful waiting.[3,4] Nevertheless, the accuracy of classifying men into groups whose cancer remained indolent versus those whose cancer progressed was
poor at all examined cut points of PSA or PSA rate of change.

**Bisphosphonates and risk of bone metastases**

Patients with locally advanced nonmetastatic disease (T2–T4, N0–N1, and M0) are at risk for developing bone metastases. Bisphosphonates are being studied as a strategy to decrease this risk.

Evidence (bisphosphonates and risk of bone metastases):

1. A placebo-controlled randomized trial (MRC-PR04) of a 5-year regimen of the first-generation bisphosphonate clodronate in high oral doses (2,080 mg per day) had no favorable impact on either time to symptomatic bone metastasis or survival.[5][Level of evidence: 1iA]

**Standard Treatment Options for Stage II Prostate Cancer**

Standard treatment options for stage II prostate cancer include the following:

1. Watchful waiting or active surveillance.
2. Radical prostatectomy.
3. External-beam radiation therapy (EBRT) with or without hormonal therapy.
   - 3-dimensional (3D) conformal radiation therapy.
4. Interstitial implantation of radioisotopes.

**Watchful waiting or active surveillance**

Asymptomatic patients of advanced age or with concomitant illness may warrant consideration of careful observation without immediate active treatment.[6-8] Watch and wait, observation, expectant management, and active surveillance are terms indicating a strategy that does not employ immediate therapy with curative intent. (Refer to the Treatment Option Overview for Prostate Cancer section of this summary for more information).

Evidence (observation with delayed hormonal therapy):

1. In a retrospective pooled analysis, 828 men with clinically localized prostate cancer were managed by initial conservative therapy with subsequent hormonal therapy given at the time of symptomatic disease progression.[6]
   - This study showed that the patients with well-differentiated tumors or moderately well-differentiated tumors experienced a disease-specific survival of 87% at 10 years and that their overall survival (OS) closely approximated the expected survival among men of similar ages in the general population.
   - The decision to treat should be made in the context of the patient’s age, associated medical illnesses, and personal desires.

**Radical prostatectomy**

Radical prostatectomy, usually with pelvic lymphadenectomy (with or without the nerve-sparing technique designed to preserve potency) is the most commonly applied therapy with curative intent.[2,9,10] Radical prostatectomy may be difficult after a transurethral resection of the prostate (TURP).

Because about 40% to 50% of men with clinically organ-confined disease are found to have pathologic extension beyond the prostate capsule or surgical margins, the role of postprostatectomy adjuvant radiation therapy has been studied.

Consideration may also be given to postoperative radiation therapy (PORT) for patients who are found to have seminal vesicle invasion by tumor at the time of prostatectomy or who have a detectable level of PSA more than 3 weeks after surgery.[11-13] Because the duration of follow-up in available studies is relatively short, the value of PORT is yet to be determined; however, PORT does reduce local recurrence.[11] Careful treatment planning is necessary to avoid morbidity.
Evidence (radical prostatectomy followed by radiation therapy):

1. In a randomized trial of 425 men with pathologic T3, N0, M0 disease, postsurgical EBRT (60–64 Gy to the prostatic fossa over 30–32 fractions) was compared with observation.[12] [Level of evidence: 1iiA]

   - The primary endpoint, metastasis-free survival, could be affected by serial PSA monitoring and resulting metastatic work-up for PSA increase. This could have biased the primary endpoint in favor of radiation therapy, which was associated with a lower rate of PSA rise. Nevertheless, metastasis-free survival was not statistically different between the two study arms \( (P = .06) \). After a median follow-up of about 10.6 years, overall median survival was 14.7 years in the radiation therapy group versus 13.8 years in the observation group \( (P = .16) \).

   - Although the OS rates were not statistically different, complication rates were substantially higher in the radiation therapy group compared with the observation group: overall complications were 23.8% versus 11.9%, rectal complications were 3.3% versus 0%, and urethral stricture was 17.8% versus 9.5%, respectively.

   - After a median follow-up of about 12.5 years, however, OS was better in the radiation therapy arm; hazard ratio \( (HR)_{\text{death}} \) of 0.72 (95% confidence interval [CI], 0.55–0.96; \( P = .023 \)). The 10-year estimated survival rates were 74% in the radiation therapy arm and 66% in the control arm. The 10-year estimated metastasis-free survivals were 73% and 65% \( (P = .016) \).[13] [Level of evidence: 1iiA]

Evidence (radical prostatectomy compared with watchful waiting):

1. In a randomized clinical trial performed in Sweden in the pre-PSA screening era, 695 men with prostate cancer were randomly assigned to radical prostatectomy versus watchful waiting. Only about 5% of the men in the trial had been diagnosed by PSA screening. Therefore, the men had more extensive local disease than is typically the case in men diagnosed with prostate cancer in the United States.[14-16]

   - The cumulative overall mortality at 18 years was 56.1% in the radical prostatectomy arm and 68.9% in the watchful waiting study arm (absolute difference, 12.7%; 95% CI, 5.1–20.3 percentage points; relative risk \( (\text{RR})_{\text{death}} \) of 0.71; 95% CI, 0.59–0.86).[16] [Level of evidence: 1iiA]

   - The cumulative incidence of prostate cancer deaths at 18 years was 17.7% versus 28.7% (absolute difference, 11.0%; 95% CI, 4.5–17.5 percentage points; \( \text{RR}_{\text{death}} \) from prostate cancer, 0.56; 95% CI, 0.41–0.77).[16]

   - In a post-hoc–subset analysis, the improvement in overall and prostate cancer-specific mortality associated with radical prostatectomy was restricted to men younger than 65 years.

2. The Prostate Intervention Versus Observation Trial (PIVOT-1 or VA-CSP-407 [NCT00002606]) is the only published randomized trial conducted in the PSA screening era that directly compared radical prostatectomy with watchful waiting. From November 1994 through January 2002, 731 men aged 75 years or younger with localized prostate cancer (stage T1–2, NX, M0, with a blood PSA <50 ng/ml) and a life expectancy of at least 10 years were randomly assigned to radical prostatectomy versus watchful waiting.[17,18] [Levels of evidence: 1iiA, 1iiB]

   - About 50% of the men had palpable tumors.

   - After a median follow-up of 10 years (range up to about 15 years), the all-cause mortality was 47.0% versus 49.9% in the radical-prostatectomy and watchful-waiting study arms, respectively, a difference that was not statistically significant (HR, 0.88; 95% CI, 0.71–1.08; \( P = .22 \)). Prostate cancer-specific mortality was 5.8% versus 8.4%, and it also was not statistically significant (HR, 0.63; 95% CI, 0.36–1.09; \( P = .09 \)).

   - Subgroup analyses showed a statistically significant reduction in overall mortality in the group of men with a baseline PSA greater than 10 ng/ml (61 of 126 men vs. 77 of 125 men; HR, 0.67) but no difference in men with a PSA of 10 ng/ml or less (110 of 238 men vs. 101 of 241 men; HR, 1.03; \( P \) for interaction = .04). Because the test for interaction was not adjusted for the numerous subgroup comparisons, it should be interpreted with caution.
Although there was a trend favoring prostatectomy, for prostate cancer-specific mortality, in men with a PSA greater than 10, the numbers were very small (7 of 126 men vs. 16 of 125 men for a PSA >10 ng/ml; 14 of 238 men vs. 15 of 241 men with lower PSA levels), and the interaction with the PSA level was not statistically significant \( (P = .11) \). There were no statistically significant differences in efficacy associated with prostatectomy by age (<65 years vs. ≥65 years), Gleason score, Charlson comorbidity status, race, or performance score.

**External-beam radiation therapy (EBRT) with or without hormonal therapy**

EBRT is another treatment option often used with curative intent.\[19-23\] Definitive radiation therapy should be delayed 4 to 6 weeks after TURP to reduce the incidence of stricture.\[24\] Adjuvant hormonal therapy should be considered for patients with bulky T2b to T2c tumors.\[25\]

The role of adjuvant hormonal therapy in patients with locally advanced disease has been analyzed by the Agency for Health Care Policy and Research (now the Agency for Healthcare Research and Quality). Most patients had more advanced disease, but patients with bulky T2b to T2c tumors were included in the studies that were re-evaluating the role of adjuvant hormonal therapy in patients with locally advanced disease.

**Evidence (EBRT with or without adjuvant hormonal therapy):**

1. The Radiation Therapy Oncology Group's (RTOG) trial 7706 (RTOG-7706).\[26\][Level of evidence: 1iiA]
   - Prophylactic radiation therapy to clinically or pathologically uninvolved pelvic lymph nodes does not appear to improve OS or prostate cancer-specific survival.

2. RTOG-9413 (RTOG-9413 [NCT00769548]) trial.\[27,28\][Level of evidence: 1iiDiii]
   - Although RTOG-9413 showed increased progression-free survival at 4 years for patients who had a 15% estimated risk of lymph node involvement and received whole-pelvic radiation therapy compared with prostate-only radiation therapy, OS and PSA failure rates were not significantly different.

3. In a randomized trial, 875 men with locally advanced nonmetastatic prostate cancer (T1b–T2 moderately or poorly differentiated tumors; T3 tumors of any grade) were randomly assigned to receive 3 months of a luteinizing hormone-releasing hormone (LH-RH) agonist plus long-term flutamide (250 mg orally 3 times a day) with or without EBRT.\[29\][Level of evidence 1iiA]
   - Nineteen percent of the men had tumor stage T2, and 78% of the men had tumor stage T3. At 10 years, both overall mortality (29.6% vs. 39.4%; 95% CI for the difference, 0.8%–18.8%) and prostate cancer-specific mortality (11.9% vs. 23.9%; 95% CI for the difference, 4.9%–19.1%) favored combined hormonal and radiation therapy.
   - Although flutamide might not be considered a standard hormonal monotherapy in the setting of T2 or T3 tumors, it is interesting to see that radiation therapy provided a disease-free survival or tumor-specific survival advantage even though this monotherapy was applied. This analysis rests on the assumption that flutamide does not shorten life expectancy and cancer-specific survival. Radiation therapy was not delivered by current standards of dose and technique.

4. Another trial compared androgen deprivation therapy (ADT: an LH-RH agonist or orchiectomy) with ADT plus radiation therapy (65–69 Gy to the prostate by 4-field box technique, including 45 Gy to the whole pelvis, seminal vesicles, and external/internal iliac nodes unless the lymph nodes were known to be histologically negative). This trial, NCIC CTG PR.3/MRC UKPRO7 [NCT00002633], from the National Cancer Institute of Canada randomly assigned 1,205 patients with high-risk (PSA >40 ng/ml or PSA >20 ng/ml and Gleason score ≥8), T2 (12%–13% of the patients), T3 (83% of the patients), and T4 (4%–5% of the patients) with clinical or pathologically staged N0, M0 disease.\[30,31\][Level of evidence; 1iiA]
   - At a median follow-up of 8 years (maximum = 13 years), OS was superior in the ADT-plus-radiation therapy group \( (HR_{\text{death}} = 0.77; \ 95\% \ CI, \ 0.57–0.85, \ P = .001) \). OS at 10 years was 55% for the ADT-plus-radiation therapy group versus 49% for the ADT-alone group.
   - Although radiation therapy had the expected bowel and urinary side effects, quality of life was the same in...
each study group by 24 months and beyond.[32]

5. A meta-analysis of randomized clinical trial evidence comparing radiation therapy with radiation therapy plus prolonged androgen suppression has been published. The meta-analysis found a difference in 5-year OS in favor of radiation therapy plus continued androgen suppression (LH-RH agonist or orchiectomy) as compared with radiation therapy alone (HR, 0.631; 95% CI, 0.479–0.831).[25][Level of evidence: 1iiA]

6. A meta-analysis of seven randomized controlled trials comparing early hormonal treatment (adjuvant or neoadjuvant) to deferred hormonal treatment (LH-RH agonists and/or antiandrogens) in patients with locally advanced prostate cancer, whether treated with prostatectomy, radiation therapy, or watchful waiting or active surveillance, showed improved overall mortality for patients receiving early treatment (RR, 0.86; 95% CI, 0.82–0.91).[33][Level of evidence: 1iiA]

7. Short-term neoadjuvant-androgen therapy administered before and during radiation therapy has shown benefit in at least some patients with clinically localized prostate cancer. In an open-label, randomized trial (RTOG-9408 [NCT00002597]), 1,979 men with nonmetastatic stage T1b–c, T2a, or T2b tumors and a PSA level of 20 ng/ml or less were randomly assigned to receive radiation therapy (66.6 Gy prostate dose in 1.8 Gy daily fractions) with or without 4 months of ADT (flutamide 250 mg by mouth 3 times per day plus either monthly goserelin 3.6 mg subcutaneously or leuprolide 7.5 mg intramuscularly), beginning 2 months before radiation therapy. Median follow-up was about 9 years.[34][Level of evidence: 1iiA]

- The 10-year OS rate was 57% in the radiation-only group versus 62% in the combined-therapy group (HRdeath of 1.17; 95% CI, 1.01–1.35; P = .03).
- In a post-hoc analysis, there was no statistically significant interaction between the treatment effect and baseline-risk category of the patients. However, there appeared to be little, if any, benefit associated with combined therapy in the lowest-risk category of patients (Gleason score ≤6; PSA ≤10 ng/ml; and clinical stage ≤T2a).
- The OS benefit was most apparent in men with intermediate-risk tumors (Gleason score 7; or Gleason score ≤6 and PSA >10 ng/ml; or clinical stage T2b).

8. The duration of neoadjuvant hormonal therapy has been tested in a randomized trial (TROG 96.01 [ACTRIN12607000237482]) involving 818 men with locally advanced (T2b, T2c, T3, and T4) nonmetastatic cancer treated with radiation therapy (i.e., 66 Gy in 2 Gy daily fractions to the prostate and seminal vesicles but not including regional lymph nodes).[35] In an open-label design, patients were randomly assigned to radiation therapy alone, 3 months of neoadjuvant androgen deprivation therapy (NADT) (goserelin 3.6 mg subcutaneously each month plus flutamide 250 mg by mouth 3 times per day) for 2 months before and during radiation, or 6 months of NADT for 5 months before and during radiation.[35][Level of evidence: 1iiA]

- After a median follow-up of 10.6 years, there were no statistically significant differences between the radiation-alone group and the radiation-plus-3-months-of NADT group.
- However, the 6-month NADT arm showed better prostate cancer-specific mortality and overall mortality than the radiation-alone group; 10-year all-cause mortality 29.2% versus 42.5% (HR, 0.63; 95% CI, 0.48–0.83, P = .0008).

9. The duration of neoadjuvant hormonal therapy was tested in another trial (RTOG 9910 [NCT00005044]) of 1,489 eligible men with intermediate-risk prostate cancer (T1b–4, Gleason score 2–6, and PSA >10 but ≤100 ng/ml; T1b–4, Gleason score 7, and PSA <20; or T1b–1c, Gleason score 8–10, and PSA <20) and no evidence of metastases. The men were randomly assigned to receive short-course neoadjuvant–androgen suppression (an LHRRH agonist plus bicalutamide or flutamide for 8 weeks before and 8 weeks during radiation therapy) or long-course neoadjuvant–androgen suppression (28 weeks before and 8 weeks during radiation therapy). Both groups received 70.2 Gy radiation in 39 daily fractions to the prostate and 46.8 Gy to the iliac lymph nodes. [36][Levels of evidence: 1iiA and 1iiB]

- After a median of 9.4 years, 10-year prostate-specific mortality, the primary endpoint, was low in both study arms: 5% versus 4% (HR, 0.81; 95% CI, 0.48–1.39).[36][Level of evidence: 1iiB]
No statistically significant differences in overall mortality or in locoregional disease progression were found. [Level of evidence: 1iiA]

There was also no apparent differential effect of androgen suppression duration among any of the risk-group subsets.

10. Addition of androgen suppression therapy to EBRT may benefit men who are at an elevated risk of disease recurrence and death from prostate cancer (RTOG-9202 [NCT00767286]).

### 3-dimensional (3D) conformal radiation therapy

EBRT designed to decrease exposure of normal tissues using methods such as CT-based 3-D conformal treatment planning is under clinical evaluation. [Level of evidence: 3iiiDiv]

### Interstitial implantation of radioisotopes

Interstitial implantation of radioisotopes (i.e., iodine-125 $^{125}$I, palladium, and iridium), using a transperineal technique with either ultrasound or computed-tomography (CT) guidance, is being done in patients with T1 or T2a tumors. Short-term results in these patients are similar to those for radical prostatectomy or EBRT. [Level of evidence: 3iiiCog]

Factors for consideration in the use of interstitial implants include the following:

- The implant is performed as outpatient surgery.
- The rate of maintenance of sexual potency with interstitial implants has been reported to be 86% to 92%. [Level of evidence: 3iiiCog]
  In contrast, rates of maintenance of sexual potency with radical prostatectomy were 10% to 40% and 40% to 60% with EBRT.
- Typical side effects from interstitial implants that are seen in most patients but subside with time include urinary tract frequency, urgency, and less commonly, urinary retention.
- Rectal ulceration may also be seen. [Level of evidence: 3iiiCog]
  In one series, a 10% 2-year actuarial genitourinary grade 2 complication rate and a 12% risk of rectal ulceration were seen. This risk decreased with increased operator experience and modification of the implant technique.

Long-term follow-up of these patients is necessary to assess treatment efficacy and side effects.

Retropubic freehand implantation with $^{125}$I has been associated with an increased local failure and complication rate and is now rarely done.

### Treatment Options Under Clinical Evaluation for Stage II Prostate Cancer

Treatment options under clinical evaluation include the following:

1. Ultrasound-guided percutaneous cryosurgery.
2. High-intensity focused ultrasound.
3. Proton-beam radiation therapy.
4. Other clinical trials.

### Ultrasound-guided percutaneous cryosurgery

Cryosurgery is a surgical technique that involves destruction of prostate cancer cells by intermittent freezing of the prostate with cryoprobes followed by thawing. [Level of evidence: 3iiiC]; [Level of evidence: 3iiiCog]

Cryosurgery is less well established than standard prostatectomy, and long-term outcomes are not as well established as with prostatectomy or radiation therapy. Serious toxic effects include:

- Bladder outlet injury.
- Urinary incontinence.
Sexual impotence.
Rectal injury.

The frequency of other side effects and the probability of cancer control at 5 years' follow-up have varied among reporting centers, and series are small compared with surgery and radiation therapy.\[^{44,45}\]

**High-intensity focused ultrasound**

High-intensity focused ultrasound has been reported in case series to produce good local disease control. However, it has not been directly compared with more standard therapies, and experience with it is more limited.\[^{46-48}\]

**Proton-beam radiation therapy**

There is growing interest in the use of proton-beam radiation therapy for the treatment of prostate cancer. Although the dose distribution of this form of charged-particle radiation has the potential to improve the therapeutic ratio of prostate radiation, allowing for an increase in dose to the tumor without a substantial increase in side effects, no randomized controlled trials have been that compare its efficacy and toxicity with those of other forms of radiation therapy.

**Other clinical trials**

Other clinical trials, including trials of neoadjuvant hormonal therapy followed by radical prostatectomy, are ongoing.

**Current Clinical Trials**

Check the list of NCI-supported cancer clinical trials that are now accepting patients with stage II prostate cancer. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.

**References**


**Stage III Prostate Cancer Treatment**

**Overview**

Stage III prostate cancer is defined by the American Joint Committee on Cancer's TNM classification system:[1]

- T3a–b, N0, M0, any prostate-specific antigen (PSA), any Gleason.

Extraprostatic extension with microscopic bladder neck invasion (T4) is included with T3a.

External-beam radiation therapy (EBRT), interstitial implantation of radioisotopes, and radical prostatectomy are used to treat stage III prostate cancer.[2] Prognosis is greatly affected by whether regional lymph nodes are evaluated and proven not to be involved.
EBRT using a linear accelerator is the most common treatment for patients with stage III prostate cancer, and large series support its success in achieving local disease control and disease-free survival (DFS).\[3,4\] The results of radical prostatectomy in stage III patients are greatly inferior compared with results in patients with stage II cancer. Interstitial implantation of radioisotopes is technically difficult in large tumors.

The patient’s symptoms related to cancer, age, and coexisting medical illnesses should be taken into account before deciding on a therapeutic plan. In a series of 372 patients treated with radiation therapy and followed for 20 years, 47% eventually died of prostate cancer, but 44% died of intercurrent illnesses without evidence of prostate cancer.\[4\]

**Standard Treatment Options for Stage III Prostate Cancer**

Standard treatment options for stage III prostate cancer include the following:

1. External-beam radiation therapy (EBRT) with or without hormonal therapy.
3. Radical prostatectomy with or without EBRT.
4. Watchful waiting or active surveillance.

**External-beam radiation therapy (EBRT) with or without hormonal therapy**

EBRT alone [3-7] or hormonal therapy luteinizing hormone-releasing hormone (LH-RH) agonist or orchiectomy) in addition to EBRT should be considered.\[8-16\] Definitive radiation therapy should be delayed until 4 to 6 weeks after transurethral resection to reduce the incidence of stricture.\[17\]

Hormonal therapy should be considered in conjunction with radiation therapy especially in men who do not have underlying moderate or severe comorbidities.\[8,9\] Several studies have investigated its utility in patients with locally advanced disease.

Evidence (EBRT with or without hormonal therapy):

1. Although patients in the RTOG-9413 (NCT00769548) trial showed a 15% estimated risk of lymph node involvement and received whole-pelvic radiation therapy compared with prostate-only radiation therapy, overall survival (OS) and PSA failure rates were not significantly different.\[18; 19\][Level of evidence: IiiDiii]

2. In a randomized trial, 875 men with locally advanced nonmetastatic prostate cancer (T1b–T2 moderately or poorly differentiated tumors; T3 tumors of any grade) were randomly assigned to receive 3 months of an LH-RH agonist plus long-term flutamide (250 mg orally 3 times a day) with or without EBRT. Nineteen percent of the men had tumor stage T2, and 78% of the men had stage T3.\[20\][Level of evidence: IiiA]
   - At 10 years, both overall mortality (29.6% vs. 39.4%; 95% confidence interval [CI] for the difference, 0.8%–8.8%) and the prostate cancer-specific mortality (11.9% vs. 23.9%; 95% CI for the difference, 4.9%–19.1%) favored combined hormonal and radiation therapy.
   - Although flutamide might not be considered a standard hormonal monotherapy in the setting of T2 or T3 tumors, it is interesting to see that radiation therapy provided a DFS or tumor-specific survival advantage even though this monotherapy was applied. This analysis rests on the assumption that flutamide does not shorten life expectancy and cancer-specific survival. Radiation therapy was not delivered by current standards of dose and technique.

3. Another trial compared androgen deprivation therapy (ADT: an LH-RH agonist or orchiectomy) to ADT plus radiation therapy (65–69 Gy to the prostate by 4-field box technique, including 45 Gy to the whole pelvis, seminal vesicles, and external/internal iliac nodes unless the lymph nodes were known to be histologically negative). This trial, NCIC (CTG PR.3/MRC UKPRT0 [NCT00002633]), from the National Cancer Institute of Canada, randomly assigned 1,205 patients with high-risk (PSA >40 ng/ml or PSA >20 ng/ml and Gleason score ≥8), T2 (12%–13% of the patients), T3 (83% of the patients), and T4 (4%–5% of the patients) with clinical or pathologically staged N0, M0 disease.\[21,22\][Level of evidence: IiiA]
   - At a median follow-up of 8 years (maximum = 13 years), OS was superior in the ADT-plus-radiation...
therapy group (hazard ratio [HR]_death 0.77; 95% CI, 0.57–0.85, \( P = .001 \)). OS at 10 years was 55% for the ADT-plus-radiation therapy group versus 49% for the ADT-alone group.

- Although radiation therapy had the expected bowel and urinary side effects, quality of life (QOL) was the same in each study group by 24 months and beyond.[23]

4. The Radiation Therapy Oncology Group (RTOG) performed a prospective randomized trial (RTOG-8531) in patients with T3, N0, or any T, N1, M0 disease who received prostatic and pelvic radiation therapy and then were randomly assigned to receive immediate adjuvant goserelin or observation with administration of goserelin at time of relapse. In patients assigned to receive adjuvant goserelin, the drug was started during the last week of the radiation therapy course and was continued indefinitely or until signs of progression.[24][Level of evidence: 1iiA]

- The actuarial 10-year OS rate for the entire population of 945 analyzable patients was 49% on the adjuvant arm versus 39% on the observation arm (\( P = .002 \)). There was also an improved actuarial 10-year local failure rate (23% vs. 38%, \( P < .001 \)).

5. A similar trial was performed by the European Organization for Research and Treatment of Cancer (EORTC). Patients with T1, T2 (World Health Organization grade 3), N0–NX or T3, T4, N0 disease were randomly assigned to receive either pelvic/prostate radiation therapy or identical radiation therapy and adjuvant goserelin (with cyproterone acetate for 1 month) starting with radiation therapy and continuing for 3 years. The 401 patients available for analysis were followed for a median of 9.1 years.[10,25][Levels of evidence: 1iiA, 1iiDii]

- The Kaplan-Meier estimates of OS at 10 years were 58.1% in the adjuvant goserelin arm and 39.8% in the radiation alone arm (\( P = .0004 \)). Similarly, 10-year DFS (47.7% vs. 22.7%, \( P < .0001 \)) and local control (94.0% vs. 76.5%, \( P < .001 \)) favored the adjuvant arm.[10,25]

- Two smaller studies, with 78 and 91 patients each, have shown similar results.[26,27]

6. The role of adjuvant hormonal therapy in patients with locally advanced disease has been analyzed by the Agency for Health Care Policy and Research (AHCPR) (now the Agency for Healthcare Research and Quality). Randomized clinical trial evidence comparing radiation therapy with radiation therapy with prolonged androgen suppression (with an LH-RH agonist or orchiectomy) was evaluated in a meta-analysis. Most patients had more advanced disease, but patients with bulky T2b tumors were included in the study.[11][Level of evidence: 1iiA]

- The meta-analysis found a difference in 5-year OS in favor of radiation therapy plus continued androgen suppression compared with radiation therapy alone (HR, 0.631; 95% CI, 0.479–0.831).[11]

7. Additionally, the RTOG did a study (RTOG-8610) in patients with bulky local disease (T2b, T2c, T3, or T4), with or without nodal involvement below the common iliac chain: 456 men were randomly assigned to receive either radiation therapy alone or radiation therapy with androgen ablation, which was started 8 weeks before radiation therapy and continued for 16 weeks. This trial assessed only short-term hormonal therapy, not long-term therapy, as the studies analyzed by the AHCPR did.[12,28]

- At 10 years, OS was not statistically significantly different; however, disease-specific mortality (23% vs. 36%) and DFS (11% vs. 3%) favored the combined treatment arm.[12][Level of evidence: 1iiA]

8. A subset analysis of the RTOG-8610 trial and the RTOG-8531 trial that involved 575 patients with T3, N0, M0 disease indicated that long-term hormones compared with short-term hormones resulted in improved biochemical DFS and cause-specific survival.[29]

9. This finding was confirmed by RTOG-9202 (NCT00767286), which reported that radiation therapy plus 28 months of androgen deprivation resulted in longer 10-year disease-specific survival (23% vs. 13%; \( P < .0001 \)) but not OS (53.9% vs. 51.6%; \( P = .36 \).[13]

- An unplanned post-hoc–subgroup analysis found increased OS with longer androgen deprivation (28 months vs. 4 months) (45% vs. 32%; \( P = .0061 \)) in men with high-grade cancers and Gleason scores of 8 through 10.

10. Likewise, a meta-analysis of seven randomized controlled trials comparing early hormonal treatment (adjuvant
or neoadjuvant) with deferred hormonal treatment (LH-RH agonists and/or antiandrogens) in patients with locally advanced prostate cancer, whether treated by prostatectomy, radiation therapy, or watchful waiting or active surveillance, showed improved overall mortality for patients receiving early treatment (relative risk, 0.86; 95% CI, 0.82–0.91).[30][Level of evidence: 1iiA]

11. The duration of neoadjuvant hormonal therapy has been tested in a randomized trial (TROG 96.01 [ACTRN12607000237482]) involving 818 men with locally advanced (T2b, T2c, T3, and T4) nonmetastatic cancer treated with radiation therapy (i.e., 66 Gy in 2 Gy daily fractions to the prostate and seminal vesicles but not including regional lymph nodes). In an open-label design, patients were randomly assigned to radiation therapy alone, 3 months of neoadjuvant androgen deprivation therapy (NADT) (goserelin 3.6 mg subcutaneously each month plus flutamide 250 mg by mouth 3 times per day) for 2 months before and during radiation, or 6 months of NADT for 5 months before and during radiation.[14][Level of evidence: 1iiA]

- After a median follow-up of 10.6 years, there were no statistically significant differences between the radiation-alone group and the radiation plus 3 months of NADT group.
- However, the 6-month NADT arm showed better prostate cancer-specific mortality and overall mortality than radiation alone; 10-year all-cause mortality 29.2% versus 42.5% (HR, 0.63; 95% CI, 0.48–0.83, P = .0008).

12. The duration of neoadjuvant hormonal therapy was tested in another trial (RTOG 9910 [NCT00005044]) of 1,489 eligible men with intermediate-risk prostate cancer (T1b–4, Gleason score 2–6, and PSA >10 but ≤100 ng/ml; T1b–4, Gleason score 7, and PSA <20; or T1b–1c, Gleason score 8–10, and PSA <20) and no evidence of metastases. The men were randomly assigned to receive short-course neoadjuvant–androgen suppression (an LHRH agonist plus bicalutamide or flutamide for 8 weeks before and 8 weeks during radiation therapy) or long-course neoadjuvant–androgen suppression (28 weeks before and 8 weeks during radiation therapy). Both groups received 70.2 Gy radiation in 39 daily fractions to the prostate and 46.8 Gy to the iliac lymph nodes.[31][Levels of evidence: 1iiA and 1iiB]

- After a median of 9.4 years, 10-year prostate-specific mortality, the primary endpoint, was low in both study arms: 5% versus 4% (HR, 0.81; 95% CI, 0.48–1.39).[31][Level of evidence: 1iiB]
- No statistically significant differences in overall mortality or in locoregional disease progression were found.[31][Level of evidence: 1iiA]
- There was also no apparent differential effect of androgen suppression duration among any of the risk-group subsets.

**Hormonal manipulations (orchiectomy or luteinizing hormone-releasing hormone [LH-RH] agonist)**

Hormonal manipulations (orchiectomy or LH-RH agonists) may be used in the treatment of stage III prostate cancer.[32][Level of evidence: 1iiA]

Antiandrogen monotherapy has also been evaluated in men with locally advanced prostate cancer as an alternative to castration.

Evidence (orchiectomy vs. LH-RH agonist):

1. In a randomized equivalence study involving 480 men with locally advanced (T3 and T4) disease, those who were treated with castration had a median OS of 70 months, whereas those treated with bicalutamide (150 mg/day) had a median OS of 63.5 months (HR, 1.05; 95% CI, 0.81–1.36); these results failed to meet the prespecified criteria for equivalence.[33][Level of evidence: 1iiA]

**Immediate versus deferred hormonal therapy**

In patients who are not candidates for or who are unwilling to undergo radical prostatectomy or radiation therapy, immediate hormonal therapy has been compared with deferred treatment (i.e., watchful waiting or active surveillance with hormonal therapy at progression).

Evidence (immediate vs. deferred hormonal therapy):
1. A randomized trial looked at immediate hormonal treatment (orchiectomy or LH-RH agonist) versus deferred treatment in men with locally advanced or asymptomatic metastatic prostate cancer.[32][Level of evidence: 1iiA]

   ○ Initial results showed better OS and prostate cancer-specific survival with the immediate treatment. This subsequently lost statistical significance as was recorded in abstract form.[34]

   ○ The incidence of pathologic fractures, spinal cord compression, and ureteric obstruction were also lower in the immediate treatment arm.

2. In another trial, 197 men with stage III or stage IV prostate cancer were randomly assigned to receive bilateral orchiectomy at diagnosis or at the time of symptomatic progression (or at the time of new metastases that were deemed likely to cause symptoms).[35][Level of evidence: 1iiA]

   ○ No statistically significant difference in OS was seen over a 12-year period of follow-up.

3. In the EORTC-30891 trial, 985 patients newly diagnosed with prostate cancer, stage T0–4, N0–2, M0, and a median age of 73 years were randomly assigned to receive androgen deprivation, either immediately or on symptomatic disease progression. The study was designed to demonstrate the noninferiority of deferred treatment as compared with immediate treatment in relation to OS.[36][Level of evidence: 1iiA]

   ○ At a median follow-up of 7.8 years, approximately 50% of the patients in the deferred treatment group had initiated androgen deprivation.

   ○ The median OS in the immediate treatment group was 7.4 years, and, in the deferred treatment group, it was 6.5 years, corresponding to a mortality HR of 1.25 (95% CI, 1.05–1.48), which failed to meet the criteria for noninferiority.

Continuous versus intermittent hormonal therapy

When used as the primary therapy for patients with stage III or stage IV prostate cancer, androgen suppression with hormonal therapy is usually given continuously until there is disease progression. Some investigators have proposed intermittent androgen suppression as a strategy to attain maximal tumor cytoreduction followed by a period without therapy to allow tumor repopulation by hormone-sensitive cells. Theoretically, this strategy might provide tumor hormone responsiveness for a longer period of time. An animal model suggested that intermittent androgen deprivation (IAD) could prolong the duration of androgen dependence of hormone-sensitive tumors.[37]

Evidence (continuous vs. intermittent hormonal therapy):

1. A systematic review of 15 randomized trials that compared continuous versus IAD therapy for patients with advanced or recurrent prostate cancer found no significant difference in OS, which was reported in eight of the trials (HR, 1.02; 95% CI, 0.93–1.11); prostate cancer-specific survival, reported in five of the trials (HR, 1.02; 95% CI, 0.87–1.19); or progression-free survival, reported in four of the trials (HR, 0.94; 95% CI, 0.84–1.05). The meta-analysis fulfilled prespecified criteria for noninferiority of OS (upper bound of 1.15 for the HR of 1.15).[38][Level of evidence: 1iiA] However, of the 15 trials, all but one had an unclear or high risk of bias according to prespecified criteria.

   ○ There was minimal difference in patient-reported QOL, but most trials found better physical and sexual functioning in patients in the IAD arms.

Radical prostatectomy with or without EBRT

Radical prostatectomy may be used with or without EBRT (in highly selected patients).[39] Because about 40% to 50% of men with clinically organ-confined disease are found to have pathologic extension beyond the prostate capsule or surgical margins, the role of postprostatectomy adjuvant radiation therapy has been studied.

Evidence (radical prostatectomy with or without EBRT):

1. In a randomized trial of 425 men with pathologic T3, N0, M0 disease, postsurgical EBRT (60–64 Gy to the prostatic fossa over 30–32 fractions) was compared with observation.[40,41]
After a median follow-up of about 12.5 years, OS was better in the radiation therapy arm; HR of death of 0.72 (95% CI, 0.55–0.96; \(P = .023\)). The 10-year estimated survival rates were 74% in the radiation therapy arm and 66% in the control arm.

The 10-year, estimated, metastasis-free survivals were 73% and 65% (\(P = .016\)).\[^{41}\][\[^{41}\][Level of evidence: \(\text{IiIA}\)]

Short-term complication rates were substantially higher in the radiation therapy group: overall complications were 23.8% versus 11.9%, rectal complications were 3.3% versus 0%, and urethral stricture was 17.8% versus 9.5%.

The role of preoperative (neoadjuvant) hormonal therapy is not established.\[^{42,43}\] Also, the morphologic changes induced by neoadjuvant androgen ablation may even complicate assessment of surgical margins and capsular involvement.\[^{44}\]

**Watchful waiting or active surveillance**

Careful observation without further immediate treatment may be used in the treatment of stage III prostate cancer.\[^{45,46}\]

Asymptomatic patients of advanced age or with concomitant illness may warrant consideration of careful observation without immediate active treatment.\[^{47-49}\] Watch and wait, observation, expectant management, and active surveillance are terms indicating a strategy that does not employ immediate therapy with curative intent. (Refer to the Treatment Option Overview for Prostate Cancer section of this summary for more information.)

**Treatment of Symptoms**

Since many stage III patients have urinary symptoms, control of symptoms is an important consideration in treatment. The following modalities may be used to improve local control of disease and subsequent symptoms:

- Radiation therapy.
- Hormonal manipulation.
- Palliative surgery (transurethral resection of the prostate [TURP]).
- Interstitial implantation combined with EBRT.
- Alternative forms of radiation therapy (under clinical evaluation).
- Ultrasound-guided percutaneous cryosurgery (under clinical evaluation).

1. Radiation therapy.\[^{3-6}\] EBRT designed to decrease exposure of normal tissues using methods such as CT-based 3D-CRT treatment planning is under clinical evaluation.

2. Hormonal manipulations effectively used as **initial** therapy for prostate cancer include the following:
   - Orchiectomy.
   - Leuprolide or other LH-RH agonists (e.g., goserelin) in daily or depot preparations. These agents may be associated with tumor flare.
   - Estrogens (diethylstilbestrol [DES] is no longer available in the United States).
   - Nonsteroidal antiandrogens (e.g., flutamide, nilutamide, and bicalutamide) or steroidal antiandrogen (e.g., cyproterone acetate).

A meta-analysis of randomized trials comparing various hormonal monotherapies in men with stage III or stage IV prostate cancer (predominantly stage IV) came to the following conclusions:\[^{50}\][Level of evidence: \(\text{IiIA}\)]

- OS at 2 years using any of the LH-RH agonists is similar to treatment with orchiectomy or 3 mg per day of DES (HR, 1.26; 95% CI, 0.92–1.39).
- Survival rates at 2 years are similar or worse with nonsteroidal antiandrogens compared with orchiectomy.
(HR, 1.22; 95% CI, 0.99–1.50).

- Treatment withdrawals, used as a surrogate for adverse effects, occurred less with LH-RH agonists (0%–4%) than with nonsteroidal antiandrogens (4%–10%).

3. Palliative surgery (TURP).

4. Interstitial implantation combined with EBRT is being used in selected T3 patients, but little information is available.[51]

5. Alternative forms of radiation therapy are being employed in clinical trials. A randomized trial from the RTOG reported improved local control and survival with mixed-beam (neutron/photon) radiation therapy compared with standard photon radiation therapy.[52] A subsequent randomized study from the same group compared fast-neutron radiation therapy with standard photon radiation therapy. Local-regional control was improved with neutron treatment, but no difference in OS was seen, although follow-up was shorter in this trial. Fewer complications were seen with the use of a multileaf collimator.[53] Proton-beam radiation therapy is also under investigation.[54]

6. Ultrasound-guided percutaneous cryosurgery is under clinical evaluation. Cryosurgery is a surgical technique under development that involves destruction of prostate cancer cells by intermittent freezing of the prostate with cryoprobes, followed by thawing.[55][Level of evidence: 3iiiC]; [56]; [57][Level of evidence: 3iiiDiv]

Cryosurgery is less well established than standard prostatectomy, and long-term outcomes are not as well established as with prostatectomy or radiation therapy. Serious toxic effects include bladder outlet injury, urinary incontinence, sexual impotence, and rectal injury. The technique of cryosurgery is under development. Impotence is common. The frequency of other side effects and the probability of cancer control at 5 years' follow-up have varied among reporting centers, and series are small compared with surgery and radiation therapy.[56,57]

**Current Clinical Trials**

Check the list of NCI-supported cancer clinical trials that are now accepting patients with stage III prostate cancer. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.

**References**


27. Granfors T, Modig H, Damber JE, et al.: Combined orchectomy and external radiotherapy versus radiotherapy alone for nonmetastatic prostate cancer with or without pelvic lymph node involvement: a prospective
Prostate Cancer Treatment (PDQ®) - PDQ Cancer Information Summa...

Stage IV Prostate Cancer Treatment

Overview

Stage IV prostate cancer is defined by the American Joint Committee on Cancer's TNM classification system:[1]

- T4, N0, M0, any prostate-specific antigen (PSA), any Gleason.
- Any T, N1, M0, any PSA, any Gleason.
- Any T, any N, M1, any PSA, any Gleason.

Extraprostatic extension with microscopic bladder neck invasion (T4) is included with T3a.

Treatment selection depends on the following factors:

- Age.
- Coexisting medical illnesses.
- Symptoms.
- The presence of distant metastases (most often bone) or regional lymph node involvement only.

The most common symptoms originate from the urinary tract or from bone metastases. Palliation of symptoms from the urinary tract with transurethral resection of the prostate (TURP) or radiation therapy and palliation of symptoms from bone metastases with radiation therapy or hormonal therapy are an important part of the management of these patients. Bisphosphonates may also be used for the management of bone metastases.[2]
Standard Treatment Options for Stage IV Prostate Cancer

Standard treatment options for stage IV prostate cancer include the following:

1. Hormonal manipulations.
2. Bisphosphonates.
3. External-beam radiation therapy (EBRT) with or without hormonal therapy.
4. Palliative radiation therapy.
5. Palliative surgery with TURP.
6. Watchful waiting or active surveillance.

Hormonal manipulations

Hormonal treatment is the mainstay of therapy for metastatic (Jewett stage D2) prostate cancer. Cure is rarely, if ever, possible, but striking subjective or objective responses to treatment occur in most patients. The addition of chemotherapy has been shown in randomized trials to improve overall survival (OS) compared with hormonal therapy alone.

In one trial, 790 patients with metastatic, hormone-sensitive disease were randomly assigned to receive androgen deprivation therapy (ADT) with or without docetaxel (75 mg/m² IV every 3 weeks for six cycles).[3] Previous adjuvant ADT was permissible if it lasted 12 months or less and progression had occurred within 12 months of completion. At a median follow-up of 28.9 months, median OS in the ADT plus docetaxel arm was 57.6 months and in the ADT-alone arm, it was 44.0 months (HRdeath 0.61; 95% CI, .47–.80; P < .001).[3][Level of evidence: 1iiA]

Hormonal manipulations effectively used as initial therapy for prostate cancer include the following:[4]

- Orchiectomy alone or with an androgen blocker as seen in the SWOG-8894 trial.
- Luteinizing hormone-releasing hormone (LH-RH) agonists, such as leuprolide in daily or depot preparations. These agents may be associated with tumor flare when used alone; therefore, the initial concomitant use of antiandrogens should be considered in the presence of liver pain, ureteral obstruction, or impending spinal cord compression.[5-8][Level of evidence: 1iiA]
- Leuprolide plus flutamide;[9] however, the addition of an antiandrogen to leuprolide has not been clearly shown in a meta-analysis to improve survival.[10]
- Estrogens (diethylstilboestrol [DES], chlorotrianisene, ethinyl estradiol, conjugated estrogens-USP and DES-diphosphate). DES is no longer commercially available in the United States.

In some series, pretreatment levels of PSA are inversely correlated with progression-free duration in patients with metastatic prostate cancer who receive hormonal therapy. After hormonal therapy is initiated, a PSA reduction to beneath a detectable level provides information regarding the duration of progression-free status; however, decreases in PSA of less than 80% may not be very predictive.[11]

Orchiectomy and estrogens yield similar results, and selection of one or the other depends on patient preference and the morbidity of expected side effects. Estrogens are associated with the development or exacerbation of cardiovascular disease, especially in high doses. DES at a dose of 1 mg per day is not associated with cardiovascular complications as frequent as those found at higher doses; however, the use of DES has decreased because of cardiovascular toxic effects. DES is no longer commercially available in the United States.

The psychological implications of orchiectomy are objectionable to many patients, and many will choose an alternative therapy if effective.[12] Combined orchiectomy and estrogens are not indicated to be superior to either treatment administered alone.[13]

A large proportion of men experience hot flushes after bilateral orchiectomy or treatment with LH-RH agonists. These hot flushes can persist for years.[14] Varying levels of success in the management of these symptoms have been reported with DES, clonidine, cyproterone acetate, or medroxyprogesterone acetate.
After tumor progression on one form of hormonal manipulation, an objective tumor response to any other form is uncommon.[15] Some studies, however, suggest that withdrawal of flutamide (with or without aminoglutethimide administration) is associated with a decline in PSA and that one may need to monitor for this response before initiating new therapy.[16-18] Low-dose prednisone may palliate symptoms in about 33% of cases.[19] Newer hormonal approaches, such as inhibition of androgen receptors, have been shown to improve OS and quality of life (QOL) after tumor progression despite ADT. (Refer to the Recurrent Prostate Cancer section of this summary for more information.)

**Immediate versus deferred hormonal therapy**

Some patients may be asymptomatic and careful observation without further immediate therapy may be appropriate.

Evidence (immediate vs. deferred hormonal therapy):

1. A meta-analysis of seven randomized controlled trials comparing early (adjuvant or neoadjuvant) with deferred hormonal treatment (LH-RH agonists and/or antiandrogens) in patients with locally advanced prostate cancer, whether treated with prostatectomy, radiation therapy, or watchful waiting or active surveillance, showed improved overall mortality with early treatment (relative risk, 0.86; 95% confidence interval (CI), 0.82–0.91). [20][Level of evidence: 1iiA]

2. In a small, randomized trial of 98 men who underwent radical prostatectomy plus pelvic lymphadenectomy and were found to have nodal metastases (stage T1–2, N1, M0), immediate continuous hormonal therapy with the LH-RH agonist goserelin or with orchiectomy was compared with deferred therapy until documentation of disease progression.[21][Level of evidence: 1iA]; [22]
   - After a median follow-up of 11.9 years, OS ($P = .04$) and prostate cancer-specific survival ($P = .004$) were superior in the immediate adjuvant therapy arm.
   - At 10 years, the survival rate in the immediate therapy arm was about 80% versus about 60% in the deferred therapy arm.[23]

3. Another trial (RTOG-8531) with twice as many randomly assigned patients showed no difference in OS with early versus late hormonal manipulation.[24]

4. Immediate hormonal therapy with goserelin or orchiectomy has also been compared with deferred hormonal therapy for clinical disease progression in a randomized trial (EORTC-30846) of men with regional lymph node involvement but no clinical evidence of metastases (any T, N+, M0). None of the 234 men had a prostatectomy or prostatic radiation therapy.[25][Level of evidence: 1iiA]
   - After a median follow-up of 8.7 years, the hazard ratio (HR) for OS in the deferred versus immediate hormonal therapy arms was 1.23 (95% CI, 0.88–1.71).
   - No statistically significant difference in OS between deferred and immediate hormonal therapy was found, but the trial was underpowered to detect small or modest differences.

5. Immediate hormonal treatment (e.g., orchiectomy or LH-RH agonist) versus deferred treatment (e.g., watchful waiting with hormonal therapy at progression) was examined in a randomized study in men with locally advanced or asymptomatic metastatic prostate cancer.[26][Level of evidence: 1iiA]
   - The initial results showed better OS and prostate cancer-specific survival with immediate treatment.
   - The incidence of pathologic fractures, spinal cord compression, and ureteric obstruction were also lower in the immediate treatment arm.

6. In another trial, 197 men with stage III or stage IV prostate cancer were randomly assigned to have a bilateral orchiectomy at diagnosis or at the time of symptomatic progression (or at the time of new metastases that were deemed likely to cause symptoms).[27][Level of evidence: 1iiA]
   - Over a 12-year period of follow-up, no statistically significant difference was observed in OS.
Approaches using LH-RH agonists or antiandrogens in patients with stage IV prostate cancer have produced response rates similar to other hormonal treatments.[5,28]

Evidence (LH-RH agonists or antiandrogens):

1. In a randomized trial, the LH-RH agonist leuprolide (1 mg subcutaneously every day) was found to be as effective as DES (3 mg orally every day) in any T, any N, M1 patients, but caused less gynecomastia, nausea and vomiting, and thromboembolisms.[6]

2. In other randomized studies, the depot LH-RH agonist goserelin was found to be as effective as orchiectomy [7,29,30] or DES at a dose of 3 mg per day.[28] A depot preparation of leuprolide, which is therapeutically equivalent to daily leuprolide, is available as a monthly or 3-monthly depot.

3. Castration has been shown to be superior to monotherapy with bicalutamide.[31]

4. A small randomized study comparing 1 mg DES orally 3 times per day with 250 mg of flutamide 3 times per day in patients with metastatic prostate cancer showed similar response rates with both regimens but superior survival with DES. More cardiovascular and/or thromboembolic toxic effects of borderline statistical significance were associated with DES treatment.[32][Level of evidence: 1iA] A variety of combinations of hormonal therapy have been tested.

**Maximal androgen blockade (MAB)**

On the basis that the adrenal glands continue to produce androgens after surgical or medical castration, case series studies were performed in which antiandrogen therapy was added to castration. Promising results from the case series led to widespread use of the strategy, known as MAB or total androgen blockade. Subsequent randomized controlled trials, however, cast doubt on the efficacy of adding an antiandrogen to castration.

Evidence (MAB):

1. In a large, randomized, controlled trial comparing treatment with bilateral orchiectomy plus either the antiandrogen flutamide or placebo, no difference in OS was reported.[33][Level of evidence: 1iA]
   - Although it has been suggested that MAB may improve the more subjective endpoint of response rate, prospectively assessed QOL was worse in the flutamide arm than in the placebo arm primarily because of more diarrhea and worse emotional function in the flutamide-treated group.[34][Level of evidence: 1iC]

2. A meta-analysis of 27 randomized trials of 8,275 patients comparing conventional surgical or medical castration with MAB—castration plus prolonged use of an antiandrogen such as flutamide, cyproterone acetate, or nilutamide—did not show a statistically significant improvement in survival associated with MAB.[10][Level of evidence: 1iA]

   When trials of androgen suppression versus androgen suppression plus either nilutamide or flutamide were examined in a subset analysis, the absolute survival rate at 5 years was better for the combined-therapy group (2.9% better, 95% CI, 0.3–5.5); however, when trials of androgen suppression versus androgen suppression plus cyproterone acetate were examined, the absolute survival trend at 5 years was worse for the combined-therapy group (2.8% worse, 95% CI, -7.6 to +2.0).[10]

3. The Agency for Health Care Policy and Research (AHCPR) (now AHRQ) has performed a systematic review of the available randomized, clinical trial evidence of single hormonal therapies and total androgen blockade performed by its Technology Evaluation Center, an evidence-based Practice Center of the Blue Cross and Blue Shield Association. A meta-analysis of randomized trials comparing various hormonal monotherapies in men with stage III or stage IV prostate cancer (predominantly stage IV) came to the following conclusions: [35][Level of evidence: 1iA]
   - OS at 2 years using any of the LH-RH agonists is similar to treatment with orchiectomy or 3 mg per day of DES (HR, 1.26; 95% CI, 0.92–1.39).
   - Survival rates at 2 years are similar or worse with nonsteroidal antiandrogens compared with orchiectomy (HR, 1.22; 95% CI, 0.99–1.50).
Treatment withdrawals, used as a surrogate for adverse effects, occurred less with LH-RH agonists (0%–4%) than with nonsteroidal antiandrogens (4%–10%).

Total androgen blockade was of no greater benefit than single hormonal therapy and with less patient tolerance. Also, the evidence was judged insufficient to determine whether men newly diagnosed with asymptomatic metastatic disease should have immediate androgen suppression therapy or should have therapy deferred until they have clinical signs or symptoms of progression.[36]

Continuous versus intermittent hormonal therapy

When used as the primary therapy for patients with stage III or stage IV prostate cancer, androgen suppression with hormonal therapy is often given continuously until there is disease progression. Another option is intermittent androgen suppression as a strategy to attain maximal tumor cytoreduction followed by a period without therapy to allow treatment-free periods. Theoretically, this strategy might provide tumor hormone responsiveness for a longer period of time. An animal model suggested that intermittent androgen deprivation (IAD) could prolong the duration of androgen dependence of hormone-sensitive tumors.[37]

Evidence (continuous vs. intermittent hormonal therapy):

1. A systematic review of 15 randomized trials that compared continuous versus intermittent ADT for patients with advanced or recurrent prostate cancer found no significant difference in OS, which was reported in eight of the trials (HR, 1.02; 95% CI, 0.93–1.11); prostate cancer-specific survival, reported in five of the trials (HR, 1.02; 95% CI, 0.87–1.19); or progression-free survival (PFS), reported in four of the trials (HR, 0.94; 95% CI, 0.84–1.05). The meta-analysis fulfilled prespecified criteria for noninferiority of OS (upper bound of 1.15 for the hazard ratio of 1.15).[38][Level of evidence: IiIA] However, of the 15 trials, all but one had an unclear or high risk of bias according to prespecified criteria.

   ○ There was minimal difference in patient-reported QOL, but most trials found better physical and sexual functioning in patients in the IAD arms.

Bisphosphonates

In addition to hormonal therapy, adjuvant treatment with bisphosphonates has been tested.[39]

Evidence (bisphosphonates):

1. In MRC-PR05, 311 men with bone metastases who were starting or responding to standard hormonal therapy were randomly assigned to oral sodium clodronate (2,080 mg per day) or a matching placebo for up to 3 years. [39][Level of evidence: IiA]

   ○ At a median follow-up of 11.5 years, OS was better in the clodronate arm: HR of death of 0.77 (95% CI, 0.60–0.98; P = .032).

   ○ Five- and 10-year survival rates were 30% and 17% in the clodronate arm versus 21% and 9% in the placebo arm.

2. A parallel study (MRC-PR04) in men with locally advanced but nonmetastatic disease showed no benefit associated with clodronate.

3. CALGB-90202 [NCT00079001] was a randomized controlled trial that compared zoledronic acid (4 mg intravenously every 4 weeks) with placebo in 645 men with androgen deprivation-sensitive prostate cancer that was metastatic to bone. Patients who progressed on hormone-therapy resistance received open-label, zoledronic acid.[40][Level of evidence: IiiDiii]

   ○ There was no difference between the two study arms in risk of the primary endpoint of time to skeletal-related events (defined as the need for palliative bone radiation, clinical fracture, spinal cord compression, bone surgery, or death from prostate cancer) after up to 7 years of follow-up.

   ○ There were also no differences in PFS or OS.
Bisphosphonates and decreasing risk of bone metastases

Patients with locally advanced nonmetastatic disease (T2–T4, N0–N1, and M0) are at risk for developing bone metastases, and bisphosphonates are being studied as a strategy to decrease this risk. However, a placebo-controlled randomized trial (MRC-PR04) of a 5-year regimen of the first-generation bisphosphonate clodronate in high oral doses (2,080 mg per day) had no favorable impact on either time to symptomatic bone metastasis or survival.[41][Level of evidence: iIA]

External-beam radiation therapy (EBRT) with or without hormonal therapy

EBRT may be used for attempted cure in highly selected stage M0 patients.[42,43] Definitive radiation therapy should be delayed 4 to 6 weeks after TURP to reduce incidence of stricture.[44]

Hormonal therapy should be considered in addition to EBRT.[36,45]

Evidence (radiation therapy with or without hormonal therapy):

1. The Blue Cross and Blue Shield Association Technology Evaluation Center, an evidence-based practice center of the Agency for Healthcare Research and Quality (AHRQ), performed a systematic review of the available randomized clinical trial evidence comparing radiation therapy with radiation therapy and prolonged androgen suppression.[36][Level of evidence: iIA] Some patients with bulky T2b tumors were included in the studied groups.
   - The meta-analysis found a difference in 5-year OS in favor of radiation therapy plus continued androgen suppression using an LH-RH agonist or orchiectomy compared with radiation therapy alone (HR, 0.63; 95% CI, 0.48–0.83).
   - This reduction in overall mortality indicates that adjuvant androgen suppression should be initiated at the time of radiation therapy and continued for several years.
   - The optimal duration of therapy and the issue of utility of neoadjuvant hormonal therapy have not been determined.

2. The duration of neoadjuvant hormonal therapy has been tested in a randomized trial (TROG 96.01 [ACTRN12607000237482]) of 818 men with locally advanced (T2b, T2c, T3, and T4), nonmetastatic cancer treated with radiation therapy (i.e., 66 Gy in 2 Gy daily fractions to the prostate and seminal vesicles but not including regional nodes). In an open-label design, patients were randomly assigned to radiation therapy alone, 3 months of neoadjuvant androgen deprivation therapy (NADT) (goserelin 3.6 mg subcutaneously each month plus flutamide 250 mg by mouth 3 times per day) for 2 months before and during radiation, or 6 months of NADT for 5 months before and during radiation.[45][Level of evidence: iIA]
   - After a median follow-up of 10.6 years, there were no statistically significant differences between the radiation alone group and the radiation plus 3 months of NADT group.
   - However, the 6-month NADT arm showed better prostate cancer-specific mortality and overall mortality than radiation alone; 10-year all-cause mortality 29.2% versus 42.5% (HR, 0.63; 95% CI, 0.48–0.83, P = .0008).

3. The duration of neoadjuvant hormonal therapy was tested in another trial (RTOG 9910 [NCT00005044]) of 1,489 eligible men with intermediate-risk prostate cancer (T1b–4, Gleason score 2–6, and PSA >10 but ≤100 ng/ml; T1b–4, Gleason score 7, and PSA <20; or T1b–1c, Gleason score 8–10, and PSA <20) and no evidence of metastases. The men were randomly assigned to receive short-course neoadjuvant–androgen suppression (an LHHR agonist plus bicalutamide or flutamide for 8 weeks before and 8 weeks during radiation therapy) or long-course neoadjuvant-androgen suppression (28 weeks before and 8 weeks during radiation therapy). Both groups received 70.2 Gy radiation in 39 daily fractions to the prostate and 46.8 Gy to the iliac lymph nodes.[46][Levels of evidence: iIA and iIB]
   - After a median of 9.4 years, 10-year prostate specific mortality, the primary endpoint, was low in both study arms: 5% versus 4% (HR, 0.81; 95% CI, 0.48–1.39).[46][Level of evidence: iIB]
No statistically significant differences in overall mortality or in locoregional disease progression were found.[46][Level of evidence: IiA]

There was also no apparent differential effect of androgen suppression duration among any of the risk-group subsets.

**Palliative radiation therapy**

A single fraction of 8 Gy has been shown to have similar benefits on bone pain relief and QOL as multiple fractions (3 Gy × 10) as was evidenced in the RTOG-9714 (NCT00003162) trial.[47][Level of evidence: IiIC] (Refer to the PDQ summary on Cancer Pain for more information.)

**Palliative surgery with transurethral resection of the prostate (TURP)**

Transurethral resection of the prostate may be useful in relieving urinary obstruction as part of palliative care in advanced prostate cancer.

**Watchful waiting or active surveillance**

Careful observation without further immediate treatment (in selected asymptomatic patients).[49]

**Treatment Options Under Clinical Evaluation for Stage IV Prostate Cancer**

Treatment options under clinical evaluation include the following:

1. Radical prostatectomy with immediate orchiectomy.
   - An uncontrolled, retrospective review of a large series of patients with any T, N1–3, M0 disease treated at the Mayo Clinic with concurrent radical prostatectomy and orchiectomy was associated with intervals to local and distant progression; however, increase in OS has not been demonstrated.[50] Patient selection factors make such study designs difficult to interpret.

**Current Clinical Trials**

Check the list of NCI-supported cancer clinical trials that are now accepting patients with stage IV prostate cancer. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.

**References**


30. Kaisary AV, Tyrrell CJ, Peeling WB, et al.: Comparison of LHRH analogue (Zoladex) with orchiectomy in


50. Zincke H: Extended experience with surgical treatment of stage D1 adenocarcinoma of prostate. Significant

Recurrent Prostate Cancer Treatment

Overview

In recurrent prostate cancer, the selection of further treatment depends on many factors, including:

- Previous treatment.
- Site of recurrence.
- Coexistent illnesses.
- Individual patient considerations.

Definitive radiation therapy can be given to patients with disease that fails only locally after prostatectomy.[1-4] An occasional patient can be salvaged with prostatectomy after a local recurrence after definitive radiation therapy;[5] however, only about 10% of patients treated initially with radiation therapy will have local relapse only. In these patients, prolonged disease control is often possible with hormonal therapy, with median cancer-specific survival of 6 years after local failure.[6]

Cryosurgical ablation of recurrence after radiation therapy is associated frequently with a high complication rate. This technique is still undergoing clinical evaluation.[7]

Hormonal therapy is used to manage most relapsing patients with disseminated disease who initially received locoregional therapy with surgery or radiation therapy. (Refer to the Standard Treatment Options for Stage IV Prostate Cancer section of this summary for more information.)

It is not clear whether additional treatments given on the basis of rising prostate-specific antigen (PSA) in asymptomatic men with prostate cancer increase overall survival (OS). Biochemical evidence of failure on the basis of elevated or rising PSA alone, therefore, may not be sufficient to alter treatment, and using surrogate endpoints for clinical decision-making is, therefore, controversial.

PSA is often used to monitor patients after initial therapy with curative intent, and elevated or rising PSA is a common trigger for additional therapy even in asymptomatic men. After radical prostatectomy, detectable PSA levels identify patients at elevated risk of local treatment failure or metastatic disease;[8] however, a substantial proportion of patients with elevated or rising PSA levels after initial therapy with curative intent may remain clinically free of symptoms for extended periods of time.[9]

1. For example, in a retrospective analysis of nearly 2,000 men who had undergone radical prostatectomy with curative intent and who were followed for a mean of 5.3 years. 315 men (15%) demonstrated an abnormal PSA of 0.2 ng/ml or higher, which is evidence of biochemical recurrence.[10]
   - Of these 315 men, 103 men (34%) developed clinical evidence of recurrence.
   - The median time to development of clinical metastasis after biochemical recurrence was 8 years.
   - After the men developed metastatic disease, the median time to death was an additional 5 years.

Likewise, after radiation therapy with curative intent, persistently elevated or rising PSA may be a prognostic factor for clinical disease recurrence. However, reported case series have used a variety of definitions of PSA failure. Criteria have been developed by the American Society for Therapeutic Radiology and Oncology Consensus Panel.[11,12] The implication of the various definitions of PSA failure for OS is not known, and as in the surgical series, many biochemical relapses (rising PSA alone) may not be clinically manifested in patients treated with radiation therapy.[13,14]

Hormonal Therapy for Recurring Disease

Continuous versus intermittent hormonal therapy
The majority of men who are treated for recurrence after initial local therapy are asymptomatic, and the recurrence is detected by a rising PSA. It is possible that intermittent androgen deprivation (IAD) therapy can be used as an alternative to continuous androgen deprivation (CAD) therapy (ADT) in an attempt to improve quality of life (QOL) and decrease the amount of time during which the patient experiences the side effects of hormonal therapy, without decreasing the survival rate.

This important clinical question was addressed in a noninferiority-designed, randomized, controlled trial with 1,386 men who had rising PSA levels (>3 ng/ml, with serum testosterone >5 nmol/L) more than 1 year after primary or salvage radiation therapy for localized prostate cancer.\[15\] Levels of evidence: 1iiA, 1iiB, 1iiC

- The ADT arm consisted of 8-month treatment cycles with a luteinizing hormone-releasing hormone (LH-RH) agonist (combined with a nonsteroidal antiandrogen for at least the first 4 weeks) that was reinstated if the PSA level exceeded 10 ng/ml. The study was powered to detect (with 95% confidence) an 8% lower OS rate in the IAD group compared with the CAD group at 7 years.
- After a median follow-up of 6.9 years (maximum follow-up 11.2 years), OS in the two groups was nearly identical, and the study was stopped (median survival 8.8 vs. 9.1 years; hazard ratio [HR]death of 1.02; 95% confidence interval [CI], 0.86–1.21). This fulfilled the prospective criterion of noninferiority.
- In a retrospective analysis, prostate cancer-specific mortality was also similar in the two arms (HR, 1.18; 95% CI, 0.90–1.55; P = 0.24). In addition, IAD was statistically significantly better than CAD in several quality-of-life domains, such as hot flashes, desire for sexual activity, and urinary symptoms. Patients on the IAD study arm received a median of 15.4 months of treatment versus 43.9 months on the CAD arm.
- The study does not address the unanswered question about whether the initiation of any ADT for an elevated PSA after initial local therapy extends survival compared with delay until clinically symptomatic progression. Of note, 59% of all deaths were unrelated to prostate cancer, and only 14% of all patients died of prostate cancer.

A systematic review of 15 randomized trials that compared continuous versus IAD therapy for patients with advanced or recurrent prostate cancer found no significant difference in OS, which was reported in eight of the trials (HR = 1.02; 95% CI, 0.93–1.11); prostate cancer-specific survival, reported in five of the trials (HR = 1.02; 95% CI, 0.87–1.19); or progression-free survival (PFS), reported in four of the trials (HR = 0.94; 95% CI, 0.84–1.05). The meta-analysis fulfilled prespecified criteria for noninferiority of OS (upper bound of 1.15 for the HR of 1.15).\[16\] Level of evidence: 1iiA However, of the 15 trials, all but one had an unclear or high risk of bias according to prespecified criteria.

- There was minimal difference in patient-reported QOL, but most trials found better physical and sexual functioning in patients in the IAD arms.

### Hormonal approaches

As noted above, studies have shown that chemotherapy with docetaxel or cabazitaxel and immunotherapy with sipuleucel-T can prolong OS in patients with hormone-resistant metastatic prostate cancer. Nevertheless, hormonal therapy has also been shown to improve survival even in men who have progressed after other forms of hormonal therapy as well as chemotherapy. Some forms of hormonal therapy are effective in the management of metastatic hormone–refractory prostate cancer.

#### Evidence (hormonal approaches):

1. Abiraterone acetate is an inhibitor of androgen biosynthesis that works by blocking cytochrome P450c17 (CYP17). Abiraterone has mineralocorticoid effects, producing an increased incidence of fluid retention and edema, hypokalemia, hypertension, and cardiac dysfunction. In addition, abiraterone is associated with hepatotoxicity.\[17\] However, compared with other therapies, abiraterone toxicities are mild. In a double-blinded placebo-controlled trial, 1,088 men with progressing hormone refractory disease (serum testosterone <50 ng per deciliter on prior antiandrogen therapy), no previous chemotherapy, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1 were given prednisone (5 mg orally twice per day) plus either abiraterone acetate (1,000 mg PO once per day) or placebo.\[18,19\] Level of evidence: 1iA The coprimary
endpoints were radiologic PFS and OS. Four sequential analyses were planned.

- At the second interim analysis, after a median follow-up of 22.2 months, the study was stopped and unblinded on the basis of aggregate efficacy and safety as assessed by the data monitoring committee. At that point, the radiologic PFS had reached the prespecified stopping boundary in favor of abiraterone: median PFS 16.5 versus 8.3 months (HR, 0.53; 95% CI, 0.45–0.62; \( P < .001 \)).

- At the fourth (and final) analysis with a median follow-up of 49.2 months (maximum 60 months), 65% had died in the abiraterone acetate study arm and 71% had died in the placebo study arm (HR, 0.81; 95% CI, 0.70–0.93; \( P = .033 \)). Median OS was 34.7 versus 30.3 months.

- Compared with placebo, abiraterone was also associated with delay in median time-to-deterioration in the FACT-P QOL score (59.9 weeks vs. 36.1 weeks, \( P < .0001 \)) and clinically important improvement in QOL in men with functional status impairment at baseline (48% vs. 32%, \( P < .0001 \)).

Men with metastatic prostate cancer who had biochemical or clinical progression after treatment with docetaxel (\( N = 1,195 \)) were randomly assigned in a 2:1 ratio to receive either abiraterone acetate (1,000 mg) (\( n = 797 \)) or placebo (\( n = 398 \)) orally once a day (COU-AA-301 [NCT00638690]). Both groups received prednisone (5 mg) orally twice a day.[21][Level of evidence; 1iA]

- After a median follow-up of 12.8 months, the trial was stopped when an interim analysis showed an OS advantage in the abiraterone group. The final report of the trial was published after a median follow-up of 20.2 months.

- Median OS was 15.8 months in the abiraterone group versus 11.2 months in the placebo group (HR of 0.74; 95% CI, 0.64–0.86; \( P < .0001 \)).

- Compared with placebo, abiraterone was also associated with delay in median time-to-deterioration in the FACT-P QOL score (59.9 weeks vs. 36.1 weeks, \( P < .0001 \)) and clinically important improvement in QOL in men with functional status impairment at baseline (48% vs. 32%, \( P < .0001 \)).

Grade 3 or worse adverse events were more common in the enzalutamide group (43% vs. 37%), primarily because of differences in hypertension, fatigue, and falls. Because patients receiving enzalutamide were on assigned therapy for an average of 1 year longer than those on placebo, the duration of response was longer in patients receiving enzalutamide, and this difference may have contributed to the increase in adverse events.

4. Enzalutamide has also been shown to increase survival in patients with progressive prostate cancer who previously received ADT as well as docetaxel. In a double-blind, placebo-controlled trial, 1,129 men were randomly assigned in a 2:1 ratio to receive enzalutamide (160 mg orally per day) versus placebo.[25–28][Levels of evidence: 1iA, 1iC]
After a median follow-up of 14.4 months, the study was stopped at the single-planned interim analysis because improved OS, the primary endpoint, was found in the enzalutamide study group (median OS, 18.4 months; 95% CI, 17.3 to not yet reached vs. 13.6 months; 95% CI, 11.3–15.8; HR of death of 0.63; 95% CI, 0.53–0.75; \( P < .001 \)). In addition, QOL, measured by the FACT-P questionnaire, was superior in the enzalutamide arm, as was time to first skeletal-related event.[26,28]

A seizure was reported in five of the 800 men in the enzalutamide study group versus none in the placebo group; however, the relationship to enzalutamide is not clear. Of the reported seizures, two patients had brain metastases, one patient had just received intravenous lidocaine, and one seizure was not witnessed.

Because there are no head-to-head comparisons, there are no trials to help decide which of these agents should be used first or in what sequence.

Even among patients with metastatic hormone-refractory prostate cancer, some heterogeneity is found in prognosis and in retained hormone sensitivity. In such patients who have symptomatic bone disease, several factors are associated with worsened prognosis: poor performance status, elevated alkaline phosphatase, abnormal serum creatinine, and short (<1 year) previous response to hormonal therapy.[29] The absolute level of PSA at the initiation of therapy in relapsed or hormone-refractory patients has not been shown to be of prognostic significance.[30]

Some patients whose disease has progressed on combined androgen blockade can respond to a variety of second-line hormonal therapies. Aminoglutethimide, hydrocortisone, flutamide withdrawal, progesterone, ketoconazole, and combinations of these therapies have produced PSA responses in 14% to 60% of patients treated and have also produced clinical responses of 0% to 25% when assessed. The duration of these PSA responses has been in the range of 2 to 4 months.[31] Survival rates are similar whether ketoconazole plus hydrocortisone is initiated at the same time as antiandrogen (e.g., flutamide, bicalutamide, or nilutamide) withdrawal or when PSA has risen after an initial trial of antiandrogen withdrawal as seen in the CLB-9583 trial, for example.[32][Level of evidence: 1iiA] Data on whether PSA changes while on chemotherapy are predictive of survival are conflicting.[30,33]

Patients treated with either luteinizing-hormone agonists or estrogens as primary therapy are generally maintained with castrate levels of testosterone. One study from ECOG showed that a superior survival resulted when patients were maintained on primary androgen deprivation;[8] however, another study from SWOG (formerly the Southwest Oncology Group) did not show an advantage to continued androgen blockade.[34]

### Prevention of bone metastases

Painful bone metastases can be a major problem for patients with prostate cancer. Many strategies have been studied for palliation, including:[35-39]

- External-beam radiation therapy (EBRT).
- Bone-seeking radionuclides (strontium chloride Sr 89).
- Denosumab (a monoclonal antibody that inhibits osteoclast function).
- Pain medication.
- Corticosteroids.
- Bisphosphonates.

(Refer to the PDQ summary on Cancer Pain for more information.)

Evidence (palliation for bone metastases using radiation therapy):

1. EBRT for palliation of bone pain can be very useful. A single fraction of 8 Gy has been shown to have similar benefits on bone pain relief and QOL as multiple fractions (3 Gy × 10) was seen in the RTOG-9714 trial, for example.[40,41][Level of evidence: 1iiC]

Evidence (palliation for bone metastases using strontium chloride):

The use of radioisotopes such as strontium chloride Sr 89 has been shown to be effective as palliative treatment of
some patients with osteoblastic metastases. As a single agent, strontium chloride Sr 89 has been reported to decrease bone pain in 80% of patients treated.[42]

1. A multicenter randomized trial of a single intravenous dose of strontium chloride Sr 89 (150 MBq: 4 mCi) versus palliative EBRT was done in men with painful bone metastases from prostate cancer despite hormone treatment.[43][Level of evidence: IiIA; [44]
   - Similar subjective pain response rates were shown in both groups: 34.7% for strontium chloride Sr 89 versus 33.3% for EBRT alone.
   - OS was better in the EBRT group than in the strontium chloride Sr 89 group ($P = .046$; median survival 11.0 months vs. 7.2 months).
   - No statistically significant differences in time-to-subjective progression or in PFS were seen.
   - When used as an adjunct to EBRT, strontium chloride Sr 89 was shown to slow disease progression and to reduce analgesic requirements, compared with EBRT alone.

Evidence (palliation or prevention of bone metastases using denosumab):

1. A placebo-controlled randomized trial (NCT00321620) compared denosumab with zoledronic acid for the prevention of skeletal events (pathologic fractures, spinal cord compression, or the need for palliative bone radiation or surgery) in men with hormonal therapy-resistant prostate cancer with at least one bone metastasis.[35]
   - The trial reported that denosumab was more effective than zoledronic acid; median time to first on-study skeletal event was 20.7 versus 17.1 months (HR, 0.82; 95% CI, 0.71–0.95).
   - Serious adverse events were reported in 63% of denosumab patients versus 60% in patients on zoledronic acid. The cumulative incidence of osteonecrosis of the jaw was low in both study arms (2% in the denosumab arm vs. 1% in the zoledronic acid arm). There was grade 3 to 4 toxicity. There was no difference in survival. The incidence of hypocalcemia was higher in the denosumab arm (13% vs. 6%).[45]

2. A randomized placebo-controlled trial included 1,432 men with castration-resistant prostate cancer with no evidence of any metastases who were given denosumab (120 mg administered subcutaneously every 4 weeks) to prevent the first evidence of bone metastasis (whether symptomatic or not).[45][Level of Evidence: IiDiii]
   - After a median follow-up of 20 months, median bone metastasis-free survival was 29.5 versus 25.2 months in the denosumab versus placebo arms (HR, 0.85; 95% CI, 0.73–0.98; $P = .028$).
   - Symptomatic bone metastases were reported in 69 (10%) denosumab patients versus 96 (13%) placebo patients (HR, 0.67; 95% CI, 0.49–0.92; $P = .01$).
   - There were no differences in OS between the two groups.
   - Osteonecrosis occurred in 33 (5%) of men on the denosumab arm versus none on the placebo arm. Hypocalcemia occurred in 12 (2%) versus 2 (<1%) men, and urinary retention in 54 (8%) of men on denosumab versus 31 (4%) of men on placebo.

**Treatment Options for Recurrent Prostate Cancer**

Treatment options for recurrent prostate cancer include the following:

- Hormone therapy.
- Chemotherapy for hormone-resistant prostate cancer.
- Immunotherapy.

**Chemotherapy for hormone-resistant prostate cancer**
Evidence (chemotherapy for hormone-resistant prostate cancer):

1. A randomized trial showed improved pain control in patients with hormone-resistant prostate cancer treated with mitoxantrone plus prednisone compared with those treated with prednisone alone.[46] Differences in OS or measured global QOL between the two treatments were not statistically significant.

2. In a randomized trial involving patients with hormone-refractory prostate cancer, docetaxel (75 mg/m² every 3 weeks) and docetaxel (30 mg weekly for 5 out of every 6 weeks) were compared with mitoxantrone (12 mg/m² every 3 weeks). All patients received oral prednisone (5 mg twice per day). Patients in the docetaxel arms also received high-dose dexamethasone pretreatment for each docetaxel administration (8 mg given at 12 hours, 3 hours, and 1 hour before the 3-week regimen; 8 mg given at 1 hour before the 5-out-of-6-weeks' regimen).[47]
   - OS at 3 years was statistically significantly better in the 3-weekly docetaxel arm (18.6%) than in the mitoxantrone arm (13.5%, HR<sub>death</sub> of 0.79; 95% CI, 0.67–0.93).
   - However, the OS rate for the 5 out-of-the-6-weeks' docetaxel regimen was 16.8%, which was not statistically significantly better than mitoxantrone.
   - QOL was also superior in the docetaxel arms compared with mitoxantrone ($P$ = .009).[48][Levels of evidence: iiA, iIC]

3. In another randomized trial involving patients with hormone-refractory prostate cancer, a 3-week regimen of estramustine (280 mg orally 3 times a day for days 1 to 5, plus daily warfarin and 325 mg aspirin to prevent vascular thrombosis), and docetaxel (60 mg/m² intravenously [IV] on day 2, preceded by dexamethasone [20 mg times 3 starting the night before]) was compared with mitoxantrone (12 mg/m² IV every 3 weeks) plus prednisone (5 mg daily).[49][Level of evidence: iIA]
   - After a median follow-up of 32 months, median OS was 17.5 months in the estramustine/docetaxel arm versus 15.6 months in the mitoxantrone arm (HR<sub>death</sub> of 0.80; 95% CI, 0.67–0.97; $P$ = .02).
   - Global QOL and pain palliation measures were similar in the two treatment arms.[50][Level of evidence: iIC]

4. A 2-weekly regimen of docetaxel has been compared with a 3-weekly regimen. OS appeared to be better in the 2-week regimen, and hematologic toxicity was less.[51][Level of evidence: iIA]
   - In the trial, 361 men with metastatic hormone-resistant prostate cancer were randomly assigned to receive docetaxel either in a 2-week regimen (50 mg/m² IV) or a 3-week regimen (75 mg/m² IV) until progression. All patients were also to receive prednisolone (10 mg by mouth daily) and dexamethasone (7.5–8.0 mg daily), starting the day before and continuing for 1 to 2 days after each docetaxel dose. Fifteen randomly assigned patients (4.2%) were thought to be ineligible in retrospect or withdrew consent, and they were dropped from the analysis.
   - With a median follow-up of 18 months, there was a small difference in time-to-treatment failure, the primary endpoint of the study (5.6 months [95% CI, 5.0–6.2] vs. 4.9 months [95% CI, 4.5–5.4]; $P$ = .014). However, there was a larger difference in median OS, a secondary endpoint, in favor of the 2-week regimen (19.5 months [95% CI, 15.9–23.1] vs. 17.0 months [95% CI, 15.0–19.1]; $P$ = .02).
   - There was a lower rate of grade 3 to 4 neutropenia with the 2-week regimen (36% vs. 53%; $P < .0001$) and a lower rate of febrile neutropenia (4% vs. 14%; $P = .001$).

5. In patients with hormone-resistant prostate cancer whose disease progressed during or after treatment with docetaxel, cabazitaxel was shown to improve survival compared with mitoxantrone in a randomized trial (NCT00417079).[52] In this trial, 755 such men were treated with daily oral prednisone (10 mg) and randomly assigned to receive either cabazitaxel (25 mg/m² IV) or mitoxantrone (12 mg/m² IV) every 3 weeks.[52][Level of evidence: iiA]
   - Median OS was 15.1 months in the cabazitaxel arm and 12.7 months in the mitoxantrone study arm (HR<sub>death</sub> of 0.70; 95% CI, 0.59–0.83; $P < .0001$).
Other chemotherapy regimens reported to produce subjective improvement in symptoms and reduction in PSA level include the following:[53][Level of evidence: 3iiiDiii]; [54]

- Paclitaxel.
- Estramustine/etoposide.
- Estramustine/vinblastine.
- Estramustine/paclitaxel.

A study suggests that patients whose tumors exhibit neuroendocrine differentiation are more responsive to chemotherapy.[55]

**Immunotherapy**

Sipuleucel-T, an active cellular immunotherapy, has been shown to increase OS in patients with hormone-refractory metastatic prostate cancer. Sipuleucel-T consists of autologous peripheral blood mononuclear cells that have been exposed ex vivo to a recombinant fusion protein (PA2024) composed of prostatic acid phosphatase fused to granulocyte-macrophage colony-stimulating factor.

Side effects are generally consistent with cytokine release and include chills, fever, headache, myalgia, sweating, and influenza-like symptoms, usually within the first 24 hours of infusion. No increase in autoimmune disorders or secondary malignancies has been noted.[56]

Evidence (immunotherapy):

1. In the largest trial (Immunotherapy for Prostate Adenocarcinoma Treatment: IMPACT trial [NCT00065442]), 512 patients with hormone-refractory metastatic disease were randomly assigned in a 2:1 ratio to receive sipuleucel-T (n = 341) versus placebo (n =171) intravenously by 60-minute infusion every 2 weeks for a total of 3 doses.[57] Patients with visceral metastases, pathologic bone fractures, or Eastern Cooperative Oncology Group (ECOG) performance status worse than 0–1 were excluded from the study. At documented disease progression, patients in the placebo group could receive, at the physician’s discretion, infusions manufactured with the same specifications as sipuleucel-T but using cells that had been cryopreserved at the time that the placebo was prepared (63.7% of the placebo patients received these transfusions). Time-to-disease progression and time to development of disease-related pain were the initial primary endpoints, but the primary endpoint was changed before unblinding based upon survival differences in two previous trials of similar design (described below).[57][Level of evidence: 1iA]

   - After a median follow-up of 34.1 months, the overall mortality was 61.6% in the sipuleucel-T group versus 70.8% in the placebo group (HR_{death} of 0.78; 95% CI, 0.61–0.98; \(P = .03\)). However, the improved survival was not accompanied by measurable antitumor effects.

   - There was no difference between the study groups in rate of disease progression. In 2011, the estimated price of sipuleucel-T was $93,000 for a 1-month course of therapy. This translates into an estimated cost of $276,000 per year-of-life saved.[58]

2. The same investigators performed two prior smaller trials (NCT00005947) of nearly identical design to the IMPACT trial.[59,60]

   - The combined results of the two smaller trials, involving a total of 225 patients randomly assigned in a 2:1 ratio of sipuleucel-T to placebo were similar to those in the IMPACT trial. The \(HR_{death}\) was 0.67 (95% CI, 0.49–0.91), but the time-to-progression rates were not statistically significantly different.

Low-dose prednisone may palliate symptoms in some patients.[61]

Evidence (low-dose prednisone for palliation):

1. A randomized comparison of prednisone (5 mg 4 times per day) with flutamide (250 mg 3 times per day) was conducted in patients with disease progression after androgen ablative therapy (castration or luteinizing...
hormone-releasing hormone agonist).[62] Prednisone and flutamide produced similar OS, symptomatic response, PSA response, and time to progression; however, there were statistically significant differences in pain, nausea and vomiting, and diarrhea in patients who received prednisone. (Refer to the PDQ summaries on Cancer Pain and Nausea and Vomiting; refer to the PDQ summary on Gastrointestinal Complications for information on diarrhea.)

Ongoing clinical trials continue to explore the value of chemotherapy for these patients.[9-12,46,53-55]

**Radiopharmaceutical Therapy**

**Alpha Emitter Radiation**

Radium-223 emits alpha particles (i.e., two protons and two neutrons bound together, identical to a helium nucleus) with a half-life of 11.4 days. It is administered intravenously and selectively taken up by newly formed bone stroma. The high-energy alpha particles have a short range of <100 mcM. Radium-223 improved OS in patients with prostate cancer metastatic to bone.

Evidence (alpha emitter radiation):

1. In a placebo-controlled trial, 921 men with symptomatic castration-resistant prostate cancer, two or more bone metastases, and no known visceral metastases, were randomly assigned in a 2:1 ratio to receive radium-223 at a dose of 50kBq per kg body weight every 4 weeks for six injections versus placebo. All study participants had already received docetaxel, were not healthy enough to receive it, or declined it.[63,64]
   - Median OS was 14.9 months in the radium-223 study group versus 11.3 months in the placebo groups (HR mortality, 0.70; 95% CI, 0.58–0.83; P < .001).[63][Level of evidence: 1iA]
   - The rates of symptomatic skeletal events (33% vs. 38%) and spinal cord compression (4% vs. 7%) were also statistically significantly improved.
   - Prospectively measured, QOL was also better in the radium-223 study group (25% vs. 16% had a ≥10 point improvement on a scale of 0 to 156; P = .02).[63][Level of evidence: 1iC]
   - With administration of radium-223 at a dose of 50kBq per kg of body weight every 4 weeks for six injections, the side effects were similar to those of a placebo.

**Current Clinical Trials**

Check the list of NCI-supported cancer clinical trials that are now accepting patients with recurrent prostate cancer. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.

**References**


46. Tannock IF, Osoba D, Stockler MR, et al.: Chemotherapy with mitoxantrone plus prednisone or prednisone


Key References for Prostate Cancer

These references have been identified by members of the PDQ Adult Treatment Editorial Board as significant in the field of prostate cancer treatment. This list is provided to inform users of important studies that have helped shape the
current understanding of and treatment options for prostate cancer. Listed after each reference are the sections within this summary where the reference is cited.

  Cited in:
  ○ Recurrent Prostate Cancer Treatment

  Cited in:
  ○ Recurrent Prostate Cancer Treatment

  Cited in:
  ○ Treatment Option Overview for Prostate Cancer
  ○ Stage II Prostate Cancer Treatment

  Cited in:
  ○ Recurrent Prostate Cancer Treatment

  Cited in:
  ○ General Information About Prostate Cancer
  ○ Treatment Option Overview for Prostate Cancer

  Cited in:
  ○ Stage II Prostate Cancer Treatment
  ○ Stage III Prostate Cancer Treatment

  Cited in:
  ○ Recurrent Prostate Cancer Treatment

  Cited in:
  ○ Treatment Option Overview for Prostate Cancer
  ○ Recurrent Prostate Cancer Treatment

Abstract

Cited in:
- Treatment Option Overview for Prostate Cancer
  Cited in:
  - General Information About Prostate Cancer
  Cited in:
  - Recurrent Prostate Cancer Treatment
  Cited in:
  - Recurrent Prostate Cancer Treatment
  Cited in:
  - Stage I Prostate Cancer Treatment
  - Stage II Prostate Cancer Treatment
  - Stage III Prostate Cancer Treatment
  - Stage IV Prostate Cancer Treatment
  Cited in:
  - Recurrent Prostate Cancer Treatment
  Cited in:
  - Stage I Prostate Cancer Treatment
  - Stage II Prostate Cancer Treatment
  - Stage III Prostate Cancer Treatment
  Cited in:
  - General Information About Prostate Cancer
  - Treatment Option Overview for Prostate Cancer
Changes to This Summary (07/05/2016)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Treatment Option Overview for Prostate Cancer

Revised text to state that on the basis of limited data from randomized trials, the more convenient schedules of hypofractionated radiation therapy appear to yield similar outcomes to conventional radiation therapy schedules, at least with respect to the intermediate outcome of disease-free survival (DFS)—a low level of evidence not known to translate into health outcomes—but potentially offering more convenient schedules of treatment (added level of evidence 1iiDiii). Added that hypofractionated radiation may incur more toxicity than standard doses, depending on the schedules used.

Added text to state that in another multicenter, randomized trial of Hypofractionated versus Conventionally Fractionated Radiotherapy for Patients with Prostate Cancer, conventional radiation therapy doses were compared with hypofractionated radiation therapy doses in a noninferiority design for hypofractionation in 820 men with intermediate- or high-risk prostate cancer (cited Aluwini et al. as reference 64). The primary efficacy endpoints are pending. Also added that with respect to toxicity, noninferiority for hypofractionated radiation therapy could not be established after a median follow-up of 5 years: cumulative genitourinary (GU) toxicity of 41.3% with hypofractionated radiation therapy versus 39% with conventional radiation therapy; gastrointestinal (GI) toxicity of 21.9% versus 17.7%; cumulative grade 3+ GU toxicity was higher in the hypofractionation group, 19.0% versus 12.9%; stool frequency was higher in the hypofractionation group, 7% versus 3%.

Added text to state that the Radiation Therapy Oncology Group reported a noninferiority trial of 1,115 men with low-risk prostate cancer who were randomly assigned to receive hypofractionated radiation therapy versus conventional radiation therapy. Also added that after a median follow-up of 5.8 years, the hypofractionated radiation therapy arm met the prospective noninferiority criterion with respect to DFS: 86.3% with hypofractionated radiation therapy versus 85.3% with conventional radiation therapy (cited Lee et al. as reference 65 and level of evidence 1iiDiii); there were 49 deaths in the hypofractionated radiation therapy arm and 51 deaths in the conventional radiation therapy arm; however, late GI grade 2+ toxicity was worse in the hypofractionated radiation therapy arm: 22.4% versus 14.0%; there was also a trend toward worse late GU grade 2+ toxicity: 29.7% versus 22.8%.

Recurrent Prostate Cancer Treatment

Added Sternberg et al. as reference 27.

Added Cella et al. as reference 28.

This summary is written and maintained by the PDQ Adult Treatment Editorial Board, which is editorially independent of NCI. The summary reflects an independent review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ® - NCI's Comprehensive Cancer Database pages.

About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the treatment of prostate cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates
This summary is reviewed regularly and updated as necessary by the PDQ Adult Treatment Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

Board members review recently published articles each month to determine whether an article should:

- be discussed at a meeting,
- be cited with text, or
- replace or update an existing article that is already cited.

Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

The lead reviewers for Prostate Cancer Treatment are:

- Timothy Gilligan, MD (Cleveland Clinic Taussig Cancer Institute)
- Barnett S. Kramer, MD (National Cancer Institute)

Any comments or questions about the summary content should be submitted to Cancer.gov through the NCI website's Email Us. Do not contact the individual Board Members with questions or comments about the summaries. Board members will not respond to individual inquiries.

**Levels of Evidence**

Some of the reference citations in this summary are accompanied by a level-of-evidence designation. These designations are intended to help readers assess the strength of the evidence supporting the use of specific interventions or approaches. The PDQ Adult Treatment Editorial Board uses a formal evidence ranking system in developing its level-of-evidence designations.

**Permission to Use This Summary**

PDQ is a registered trademark. Although the content of PDQ documents can be used freely as text, it cannot be identified as an NCI PDQ cancer information summary unless it is presented in its entirety and is regularly updated. However, an author would be permitted to write a sentence such as “NCI’s PDQ cancer information summary about breast cancer prevention states the risks succinctly: [include excerpt from the summary].”

The preferred citation for this PDQ summary is:


Images in this summary are used with permission of the author(s), artist, and/or publisher for use within the PDQ summaries only. Permission to use images outside the context of PDQ information must be obtained from the owner(s) and cannot be granted by the National Cancer Institute. Information about using the illustrations in this summary, along with many other cancer-related images, is available in Visuals Online, a collection of over 2,000 scientific images.

**Disclaimer**

Based on the strength of the available evidence, treatment options may be described as either “standard” or “under clinical evaluation.” These classifications should not be used as a basis for insurance reimbursement determinations. More information on insurance coverage is available on Cancer.gov on the Managing Cancer Care page.

**Contact Us**

More information about contacting us or receiving help with the Cancer.gov website can be found on our Contact Us for Help page. Questions can also be submitted to Cancer.gov through the website’s Email Us.