

Treatments for Clinically Localized Prostate Cancer



This guide summarizes clinical evidence comparing the effectiveness and safety of treatments for clinically localized prostate cancer. It discusses expectant management and three active treatments (radical prostatectomy, radiation therapy, and hormonal therapy). This guide does not cover nutritional supplements. It also does not cover some newer treatments (cryotherapy, high-intensity focused ultrasound, and laparoscopic or robotic-assisted prostatectomy) for which there is little research about comparative effectiveness. This guide does not address strategies to prevent or screen for prostate cancer or strategies to treat advanced prostate cancer.

CLINICAL ISSUE

Prostate cancer is common and primarily affects men older than 65. About 90 percent of men diagnosed with prostate cancer will have clinically localized disease (cancers confined to the prostate gland).

Since the early 1990s, both the number of men screened with the prostate specific antigen (PSA) blood test and the incidence of newly diagnosed cases have increased substantially.

PSA screening detects cancers earlier and of smaller size than other clinical methods. Increased detection of localized disease has led to more frequent intervention with treatments that are potentially effective but have side effects.

Treatment approaches vary by geographic region of the United States and by physician specialty. The reasons for this variation are not clear and are not strongly linked to tumor grade (Gleason score) or PSA levels.

This guide provides research evidence to help clinicians work with patients to manage localized prostate cancer. Most long-term evidence about treatments comes from followup of men whose cancers were detected prior to widespread PSA screening.

The long-term outcomes of treatments for men with PSA-detected disease are not yet available and may be different than the results summarized in this guide.

SOURCE The source material for this guide is a systematic review of 592 research publications. The review, *Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer* (2008), was prepared by the Minnesota Evidence-based Practice Center. The Agency for Healthcare Research and Quality (AHRQ) funded the systematic review and this guide. The guide was developed using feedback from clinicians who reviewed preliminary drafts.

CONFIDENCE SCALE

The confidence ratings in this guide are derived from a systematic review of the literature. The level of confidence is based on the overall quantity and quality of clinical evidence.

HIGH ●●● There are consistent results from good quality studies. Further research is very unlikely to change the conclusions.

MEDIUM ●●○ Findings are supported, but further research could change the conclusions.

LOW ●○○ There are very few studies, or existing studies are flawed.

CLINICAL BOTTOM LINE

- Men whose tumors have high Gleason scores have higher rates of cancer recurrence and death than men who have tumors with low Gleason scores. This is true no matter what treatments are used.

LEVEL OF CONFIDENCE ●●●

- Men who have radical prostatectomy for localized prostate cancer are less likely to develop distant metastases or die from the cancer than men who use expectant management.

LEVEL OF CONFIDENCE ●●○

- Radical prostatectomy, radiation therapy, and hormonal therapy result in more long-term side effects than expectant management. These include sexual, urinary, and bowel problems.

LEVEL OF CONFIDENCE ●●●

- Evidence is insufficient to determine whether radiation or hormonal therapy results in fewer deaths or cancer progressions than expectant management.

- Evidence is insufficient to determine whether any type of radiation therapy results in fewer deaths or cancer recurrences than radical prostatectomy.

TREATMENT OPTIONS

The first treatment decision is generally whether to use expectant management or an active treatment. As most men diagnosed with localized prostate cancer die from other causes, quality of life is an important consideration. Weighing the options includes considering the benefits and risks of active treatment compared with expectant management in light of individual factors such as age, health status, Gleason score, PSA level, and patient preferences. Radical prostatectomy and radiation therapy are the most commonly used active treatments. Hormonal therapy is usually adjuvant therapy to prostatectomy or radiation, although it is sometimes used as the sole initial therapy for localized prostate cancer.

Gleason Scores

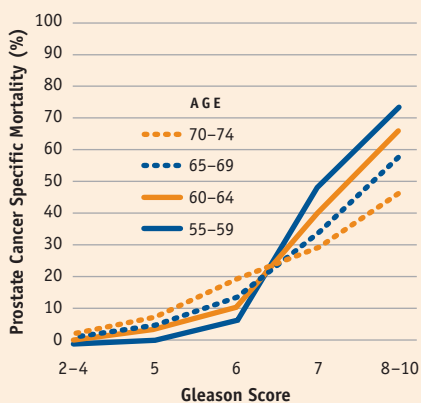
Gleason scores range from 2 to 10 and measure the aggressiveness of the cancer. Tumors with scores of 8–10 are most aggressive.

Higher Gleason scores are associated with greater risk of recurrence, progression, and death from prostate cancer, regardless of the type of treatment.

LEVEL OF CONFIDENCE ●●●

In estimating the risk of cancer progression, Gleason score is often considered along with the PSA level.

Figure 1. Effect of Gleason Score and Age on 10-Year Prostate Cancer Specific Mortality¹

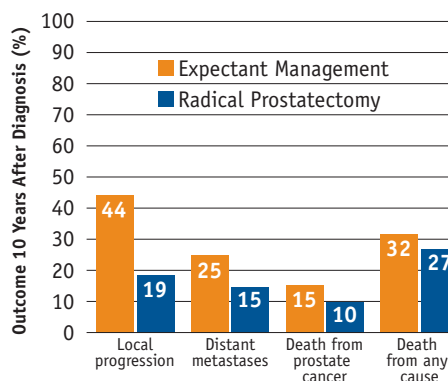


¹ Results are from a large study of men diagnosed between 1971 and 1984. Men initially used expectant management or hormonal therapy. The cancers were not diagnosed by PSA testing. (JAMA 2005;293:2095-101.)

Expectant Management

With expectant management (also known as watchful waiting or active surveillance), men have regular monitoring of their prostate cancer. Monitoring may include PSA testing, digital rectal examination, prostate ultrasound, or prostate biopsy. If the cancer progresses, an active treatment can be added.

Figure 2. Radical Prostatectomy Versus Expectant Management¹



¹ Results are from a large, randomized controlled trial of men diagnosed between 1989 and 1999. Average age at diagnosis was 65 years, average Gleason score 5–6, and average PSA 13 ng/mL. Most cancers were not diagnosed by PSA testing. Men in both groups who had local progression received hormonal therapy. (N Engl J Med 2005;352:1977-84.)

Radical Prostatectomy

Radical prostatectomy is the most widely used surgical treatment for prostate cancer. Men who are initially treated with radical prostatectomy tend to be younger and report better health status than men initially treated with radiation therapy or hormonal therapy. They also tend to be younger and healthier than men who use expectant management. Evidence is insufficient to determine whether older men attain the same benefits from radical prostatectomy as younger men.

Risks of surgery increase with age. Treatment-related problems are also common in older men. Up to 10 percent of men 65 and older experience cardio-pulmonary complications after surgery.

Most prostatectomies involve lower abdominal incision. Nerve-sparing surgical techniques are widely used and are designed to lessen the chance of erectile dysfunction (ED). Evidence is insufficient to judge whether newer techniques, such as laparoscopic or robotic-assisted prostatectomy, are as effective as conventional surgery.

- Men who have radical prostatectomy for localized prostate cancer are less likely to die from prostate cancer than men who use expectant management. (See Figure 2.)

LEVEL OF CONFIDENCE ●●○

- Using hormonal therapy before prostatectomy (neoadjuvant hormonal therapy) does not improve survival or cancer recurrence rates compared with prostatectomy alone.

LEVEL OF CONFIDENCE ●●○

Radiation Therapy

Two types of radiation therapy are currently in wide use: external beam radiation therapy (EBRT) and brachytherapy (radioactive seeds implanted into the prostate). Recent modifications to EBRT include conformal EBRT and intensity-modulated radiation therapy (IMRT). These techniques focus on delivering radiation to the cancer cells while minimizing damage to healthy tissue.

- Increasing the total amount of radiation slows the rate of cancer progression (as measured by PSA levels) compared with lower doses of radiation therapy. Higher total EBRT doses do not increase urinary side effects but can increase gastrointestinal side effects.

LEVEL OF CONFIDENCE ● ● ○

- Evidence is insufficient to determine whether higher doses of radiation reduce mortality compared with lower doses of radiation.
 - Combining 6 months of hormonal therapy (leuprolide or goserelin, combined with flutamide) with EBRT can reduce mortality but increases side effects. One study found that 12 percent of men treated with combination therapy and 22 percent of men treated with EBRT alone had died from any cause within 5 years.
- LEVEL OF CONFIDENCE ● ● ○
- It is not known how the results of treatment with any type of radiation therapy compare with the results of expectant management or radical prostatectomy.
 - Evidence is insufficient to determine whether the results of other radiation modalities (brachytherapy, proton beam, or IMRT) differ from the results of conventional EBRT.

Hormonal Therapy

Reducing the effects of testosterone slows the growth of prostate cancer. Hormonal therapy includes surgical orchiectomy, androgen-blocking agents (such as flutamide and bicalutamide), and hormonal agonists (such as leuprolide and goserelin).

Hormonal therapy is usually an adjuvant or salvage therapy, but it is sometimes used as sole initial therapy.

- Bicalutamide (used alone or in addition to prostatectomy or EBRT) does not reduce cancer recurrence or mortality.

LEVEL OF CONFIDENCE ● ● ○

- There is insufficient evidence about the effectiveness of using other hormonal therapies to treat localized prostate cancer.

SIDE EFFECTS

All the active treatments cause short-term and long-term side effects. ED, urinary problems, and bowel problems are common.

Erectile Dysfunction

Inability to achieve and maintain an erection is the most common long-term side effect and occurs with all active prostate cancer treatments.

LEVEL OF CONFIDENCE ● ● ●

Urinary Problems

Incontinence is more common after prostatectomy than after radiation or hormonal therapy.

LEVEL OF CONFIDENCE ● ● ●

Bowel Problems

Bowel problems, such as painful hemorrhoids and bowel urgency, are more common after EBRT than after other treatments.

LEVEL OF CONFIDENCE ● ● ●

Comparing Side Effects 2 Years After Treatment¹

Treatment	Expectant Management	Radical Prostatectomy	EBRT	Hormonal Therapy
Erectile Dysfunction (no erections at all)	33%	58%	43%	86%
Urinary Leakage (daily or more often)	7%	35%	12%	11%
Bowel Urgency (some days)	16%	14%	29%	16%

¹ Results are from a large population-based survey of men with prostate cancer in the United States. (Cancer 2003;97:1653-62.)

Effects of Hormonal Therapy

Hormonal therapy can cause loss of libido, depression, memory difficulties, fatigue, hot flashes, gynecomastia, and fractures.

- **Hot Flashes.** About 60 percent of men have hot flashes with hormonal therapy (hormonal agonist or orchiectomy).

LEVEL OF CONFIDENCE ● ● ○

- **Gynecomastia.** About 25 percent of men taking a hormonal agonist and 10 percent of men treated with orchiectomy have breast swelling.

LEVEL OF CONFIDENCE ● ● ○

- **Fractures.** At 5 years after diagnosis, men treated with hormonal therapy have more fractures than men not treated with hormonal therapy (19 percent versus 13 percent). The risk of fracture increases with the total number of doses of hormonal therapy.

LEVEL OF CONFIDENCE ● ● ○

- Men receiving 6 months of hormonal therapy with EBRT have more gynecomastia and ED (erections not sufficient for intercourse) than men treated with EBRT alone.

LEVEL OF CONFIDENCE ● ● ○

CHOOSING AN APPROACH

The primary decision is whether to choose expectant management or active treatment. If active treatment is pursued, there is limited comparative evidence to guide the choice. Most of this evidence is derived from studies comparing single treatments with expectant management and from observational studies about side effects. Patient preferences are an important factor in determining a management strategy.

Expectant Management Versus Active Treatments

Age and Health Status

The survival benefit of any prostate cancer treatment becomes apparent years after treatment. Men who have a shorter life expectancy due to advanced age or serious medical problems are less likely to benefit from initial active treatment.

Gleason Score

Men whose tumors have a high Gleason score (8–10) have a higher probability of early tumor progression. If these men use expectant management, they may face further treatment decisions when their tumors progress. Men with more aggressive cancers may be inclined to pursue an active treatment. However, based on the review, we do not know if an active treatment reduces tumor progression or mortality compared with expectant management.

Choosing Among Active Treatments

- Men who have radical prostatectomy generally have a lower risk of cancer progression and death than men who follow expectant management.
- It is not known whether men who undergo any type of radiation therapy have a higher risk of death than men who undergo radical prostatectomy or expectant management.
- Bicalutamide is not effective as initial treatment. There is no evidence about the effectiveness of using other hormonal therapy as sole initial treatment for localized prostate cancer.
- The long-term outcomes for many newer treatment approaches (cryotherapy, high-intensity focused ultrasound, and laparoscopic or robotic-assisted prostatectomy) are not yet known.

Volume and Outcomes

- Men treated in higher volume hospitals (43 or more prostatectomies per year) have fewer complications than men treated in hospitals that perform fewer prostatectomies.

LEVEL OF CONFIDENCE ● ● ○

- Men treated by higher volume surgeons (10 or more prostatectomies per year) have lower rates of urinary complications and incontinence than men treated by surgeons who perform fewer prostatectomies.

LEVEL OF CONFIDENCE ● ● ○

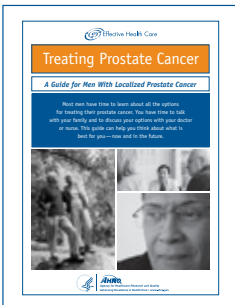
Combination Therapy

Consider combining hormonal therapy with radiation. Combining 6 months of hormonal therapy with radiation improves survival.

Side Effects

All active treatments can cause temporary and permanent side effects. Presenting the risks of these side effects can help men make their treatment decisions.

RESOURCE FOR PATIENTS



Treating Prostate Cancer: A Guide for Men With Localized Prostate Cancer is a companion to this Clinician's Guide. It can help men talk with their

health care professional about treatment options for prostate cancer.

FOR MORE INFORMATION

For electronic copies of the consumer's guide, this clinician's guide, and the full systematic review, visit this Web site: www.effectivehealthcare.ahrq.gov

For free print copies call:

The AHRQ Publications Clearinghouse (800) 358-9295

Consumer's Guide,
AHRQ Pub. No. 08-EHC010-2A

Clinician's Guide,
AHRQ Pub. No. 08-EHC010-3

ON THE HORIZON

Results are due soon for a study that compares cryotherapy with EBRT. Results from the PIVOT trial comparing radical prostatectomy with expectant management are due after 2010. The ProtecT study, which compares radical prostatectomy, EBRT, and expectant management, is recruiting.

AHRQ created the John M. Eisenberg Center at Oregon Health & Science University to make research useful for decisionmakers. This guide was prepared by Monica Goei, M.D., David Hickam, M.D., Sandra Robinson, M.S.P.H., Martha Schechtel, R.N., Erin Davis, B.A., and Valerie King, M.D., of the Eisenberg Center.