

Review

Comparative Evaluation of Radiation Treatments for Clinically Localized Prostate Cancer: An Updated Systematic Review

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Abstract

Background: Radiation therapy is one of many treatment options for patients with prostate cancer.

Purpose: To update findings about the clinical and biochemical outcomes of radiation therapies for localized prostate cancer.

Data Sources: MEDLINE (2007 through March 2011) and the Cochrane Central Register of Controlled Trials (2007 through March 2011).

Study Selection: Published English-language comparative studies involving adults with localized prostate cancer who either had first-line radiation therapy or received no initial treatment.

Data Extraction: 6 researchers extracted information on study design, potential bias, sample characteristics, interventions, and outcomes and rated the strength of overall evidence. Data for each study were extracted by 1 reviewer and confirmed by another.

Data Synthesis: 75 studies (10 randomized, controlled trials [RCTs] and 65 nonrandomized studies) met inclusion criteria. No RCTs compared radiation therapy with no treatment or no initial treatment. Among the 10 RCTs, 2 compared combinations of radiation therapies, 7 compared doses and fraction sizes of external-beam radiation therapy (EBRT), and 1 compared forms of low-dose rate radiation therapy. Heterogeneous outcomes were analyzed. Overall, moderate-strength evidence consistently showed that a higher EBRT dose was associated with increased rates of long-term biochemical control compared with lower EBRT dose. The body of evidence was rated as insufficient for all other comparisons.

Limitations: Studies inconsistently defined and reported outcomes. Much of the available evidence comes from observational studies with treatment selection biases.

Conclusion: A lack of high-quality comparative evidence precludes conclusions about the efficacy of radiation treatments compared with no treatments for localized prostate cancer.

Primary Funding Source: Agency for Healthcare Research and Quality.

Editors' Notes

Context

- Is radiation therapy an effective treatment for localized prostate cancer?

Contribution

- This review found inadequate evidence about survival benefits for radiation therapy compared with no treatment for localized prostate cancer. Data regarding the comparative effectiveness of different radiotherapies was also insufficient, except that higher external-beam radiation therapy (EBRT) dose was associated with better long-term biochemical control than was lower EBRT dose. Radiation therapies sometimes caused urinary or bowel problems, and brachytherapy seemed associated with more urinary toxicity than EBRT.

Implication

- Whether or which radiation treatments improve clinical outcomes for men with localized prostate cancer is unknown.

—The Editors

Prostate cancer is the most common noncutaneous cancer diagnosed in men in the United States. The American Cancer Society estimates that in 2009 approximately 192 000 men received a prostate cancer diagnosis and approximately 27 000 men died of the disease (1). Widespread prostate-specific antigen (PSA) testing has doubled the incidence of prostate cancer and the lifetime risk for prostate cancer to approximately 16% (2). Prostate cancer is also diagnosed earlier, and the incidence of clinically “silent” T1 tumors has increased from 17% in 1989 to 48% in 2001 (3) since the advent of PSA screening. Overall, the vast majority of patients with prostate cancer diagnoses today have clinically localized prostate cancer (T1–T2N0).

Depending on a patient’s risk profile, many treatment options are available, including active surveillance or watchful waiting, surgery, radiation therapy, cryotherapy, high-intensity focused ultrasonography, and androgen deprivation therapy (ADT). In 2008, the Agency for Healthcare Research and Quality published a systematic review comparing all of the treatment options (4), which concluded that no one therapy can be considered the preferred treatment because of limitations in the available evidence and tradeoffs between effectiveness and adverse effects. Recently, the Coverage and Analysis Group at the Centers for Medicare & Medicaid Services commissioned the Agency for Healthcare Research and Quality to update the report. The Agency for Healthcare Research and Quality requested the Tufts Evidence-based Practice Center to conduct an update specifically reviewing the comparative effectiveness of radiation treatments for patients with localized prostate cancer.

Methods

We used methods adapted from the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews, version 1.0, published by the Agency for Healthcare Research and Quality (5). A full technical report that describes methods in detail, including literature search strategies, and results, including evidence tables, is available elsewhere (6).

Key Questions

We focused this report on 2 key questions:

1. What are the benefits and harms of radiation therapy for clinically localized prostate cancer compared with no treatment or no initial treatment (watchful waiting, active surveillance, or observation)?
2. What are the benefits and harms of different forms of radiation therapy for clinically localized prostate cancer?

Data Sources and Searches

We searched MEDLINE and the Cochrane Central Register of Controlled Trials from January 2007 to 11 March 2011 for studies in adults with clinically

localized prostate cancer who had radiation treatments. We combined search terms or Medical Subject Heading terms for prostate neoplasm and terms relevant to radiation therapy (for example, *proton beam*, *particle beam*, *external beam*, *radiotherapy*, *intensity-modulated radiotherapy*, *brachytherapy*), and we limited our search to English-language reports of primary studies in adults that were published in peer-reviewed journals. We also used the previous review to identify randomized, controlled trials (RCTs) published before 2007 (4).

Study Selection

We included only RCTs and nonrandomized comparative studies. We excluded single-cohort studies, case reports, and conference abstracts.

Patient Populations of Interest

We included studies of men with clinically localized prostate cancer (T1–T2, N0–X, M0–X) regardless of age, histologic grade, or PSA level. We excluded studies in which more than 20% of patients had locally advanced (T3–T4) cancer; adjuvant, salvage, or postprostatectomy radiation therapy studies; and studies specifically evaluating ADT in conjunction with radiation therapy.

Interventions and Comparators of Interest

The intervention of interest was radiation treatment used as first-line treatment of prostate cancer, including external-beam radiation therapy (EBRT) (conformal radiation, intensity-modulated radiotherapy, or proton therapy), stereotactic body radiation therapy (SBRT), and brachytherapy (low-dose rate [permanent seed implantation] brachytherapy [LDRBT] and high-dose rate temporary brachytherapy [HDRBT]). We also included combination radiation therapies, such as EBRT with brachytherapy boost.

Comparators of interest were no treatment or no initial treatment or different forms of radiation therapy.

Outcomes of Interest

We included studies that reported either clinical or biochemical outcomes. Outcomes of interest included overall survival, prostate cancer-specific survival, metastases- and/or clinical progression-free survival, biochemical failure, health status, and quality of life.

Data Extraction and Quality Assessment

Six researchers participated in abstracting the studies. Data from each study were extracted by 1 of the reviewers and confirmed by another. The extracted data included information on patient samples, radiation treatment characteristics, clinical and biochemical outcomes, adverse events, and study design. For most outcomes, data from 5 years, 10 years, and/or the last reported time point were included. We also evaluated study quality and potential sources of bias with respect to adequate power, randomization, blinding, allocation concealment, intention-to-treat analysis, adequate length of follow-up, number of dropouts, and loss to follow-up. We rated the strength of the overall body of evidence for each comparison as high, moderate, or insufficient (5). The strength of the overall body of evidence was rated by the entire group of reviewers, and disagreements were resolved by consensus.

Data Synthesis and Analysis

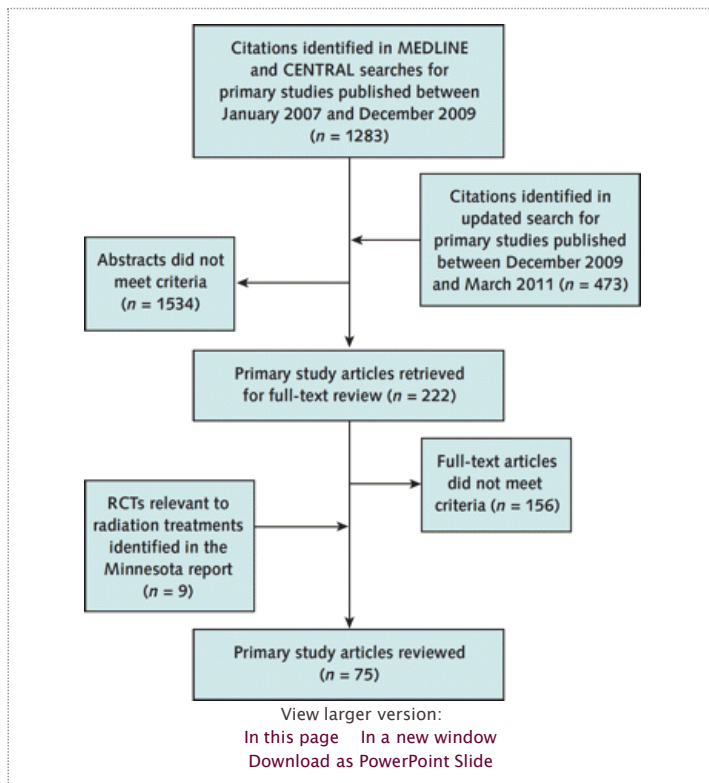
For clinical outcomes, we calculated the risk or rate difference to quantify the effect size. For adverse events, most studies used the Radiation Therapy Oncology Group adverse event classification scheme (7, 8) in reporting urinary and bowel toxicities. We enumerated only grade 3 or greater events.

Role of the Funding Source

The Agency for Healthcare Research and Quality provided funding for this work. The funding source helped formulate the initial study questions but did not participate in the literature search; determination of study eligibility criteria; data analysis or interpretation; or preparation, review, or approval of the manuscript for publication.

Results

We screened 1756 abstracts and evaluated 222 full-text articles ([Appendix Figure](#)); 66 studies from the searches met eligibility criteria. Including 9 RCTs from the earlier 2008 review, a total of 75 articles were analyzed: 10 RCTs and 65 nonrandomized comparative studies. [Table 1](#) summarizes the characteristics of the included RCTs (in 14 publications [9–22]).



Appendix Figure. Summary of evidence search and selection.

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CENTRAL = Cochrane Central Register of Controlled Trials; RCT = randomized, controlled trial.

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Table 1. Characteristics of Randomized, Controlled Trials Comparing Radiation Treatments for Clinically Localized Prostate Cancer

Radiation Therapy Versus No Treatment or No Initial Treatment

No RCT compared the effectiveness between any form of radiation therapy and no treatment or no initial treatment ([Table 2](#)). One prospective study compared EBRT with no treatment or no initial treatment by using modeling and reported significantly worse sexual function in the former over 6 to 24 months of follow-up ($P < 0.05$); no statistically significant difference was found between brachytherapy and no treatment or no initial treatment (23). Four of 8

retrospective studies that compared some form of radiation therapy with no treatment or no initial treatment (24–31) reported on disease-specific survival. One found a statistically significant improvement in patients who received brachytherapy compared with no treatment or no initial treatment (adjusted hazard ratio [HR], 0.45 [95% CI, 0.23 to 0.87]) (28). Of the 3 studies reporting on urinary and bowel function after radiation therapy compared with no treatment or no initial treatment (26, 29, 31), 1 found a higher rate of urethral strictures in patients treated with combined EBRT and brachytherapy (adjusted HR, 4.56 [CI, 1.23 to 16.88]) (26), 1 provided indirect data suggesting that patients treated with EBRT might have worse bowel function (29), and 1 reported significantly worse bowel function in patients who received radiation therapy (transformed Expanded Prostate Cancer Index Composite score, 87.1 vs. 92.8, respectively; $P < 0.001$) (31). One other study found statistically significantly higher rates of second primary cancer in patients treated with EBRT compared with no treatment (adjusted HR, 1.14 [CI, 1.09 to 1.19]) (24).

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Table 2. Summary of Evidence on Outcomes of Therapies for Clinically Localized Prostate Cancer

Comparisons Between Radiation Treatments

Six prospective studies (7 publications [23, 32–37]) and 9 retrospective studies (28, 38–45) compared LDRBT with EBRT (Table 2). Among the prospective studies, none evaluated disease control, and outcomes for urinary and bowel toxicities and sexual dysfunction were mostly inconclusive. The 1 retrospective study that reported on disease-specific survival did not find a statistically significant difference between groups at 7 years (28). Results of retrospective studies were inconclusive regarding freedom from biochemical failure (38, 41–45), urinary toxicities (42, 43, 45), and bowel toxicities (40, 42, 43, 45).

One retrospective study compared HDRBT (38 Gy or 42 Gy) with LDRBT (46) and reported no statistically significant differences in freedom from biochemical failure at 5 years, bowel and urinary toxicities, and sexual dysfunction. No studies compared SBRT with any other radiation method or HDRBT with EBRT.

Comparisons of Combinations of Radiation Therapies

Fifteen studies, including 2 RCTs, compared combinations of EBRT and brachytherapy (9, 10, 24, 26, 45, 47–56) (Tables 1 and 2 and Appendix Tables 1 and 2). One small trial reported that the combination of EBRT and brachytherapy had lower biochemical or clinical failure rates at 5 years (adjusted HR, 0.37 [CI, 0.16 to 0.85]) than EBRT alone (9). The other trial did not find statistically significant differences in biochemical failure rates when comparing LDRBT plus EBRT in 2 different doses (10).

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Appendix Table 1. Randomized, Controlled Trials Comparing Radiation Treatments for Clinically Localized Prostate Cancer and Reporting Freedom From Biochemical Failure [↗ Web-Only](#)

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Appendix Table 2. Results for the Comparisons in Combination Therapies [↗ Web-Only](#)

Several cohort studies reported results related to freedom from biochemical

failure or urinary or bowel toxicities (24, 26, 45, 47–56). For freedom from biochemical failure, 1 study favored LDRBT plus EBRT over LDRBT at 8 years (96% vs. 72%; $P = 0.015$) (53); 1 study favored high-dose HDRBT plus EBRT over low-dose HDRBT plus EBRT at 10 years (81% vs. 57%; $P < 0.001$) (56); and 1 study reported prostate cancer relapse-free survival at 5 years and favored HDRBT plus EBRT over EBRT (98% vs. 82%; $P < 0.001$) (54). Concerning urinary toxicity, 1 study found an increase in late urinary toxicity in LDRBT plus EBRT compared with EBRT (18% vs. 5%; $P < 0.05$) (45), and 1 study found an increase in urethral strictures in brachytherapy plus EBRT compared with EBRT (5.2% vs. 1.7%; $P < 0.05$) (26). Finally, 1 study that compared EBRT alone with EBRT plus brachytherapy showed an increase in cases of second primary cancer (10.3% vs. 5.7%; $P < 0.001$) and late (≥ 5 years) second primary cancer (4.2% vs. 1.4%; $P < 0.001$) in the former versus latter therapy (24).

Comparisons Within a Given Radiation Treatment

Intra-SBRT Comparisons

One retrospective study compared SBRT of 35 Gy in 5 fractions with 36.25 Gy in 5 fractions and found no statistically significant difference in late bowel and urinary toxicities at 30 months (57).

Intra-EBRT Comparisons

Three RCTs (7 publications [11–15, 58, 59]), 2 prospective studies (60, 61), and 9 retrospective studies (45, 62–70) compared conventional-dose with high-dose EBRT (maximum, 86 Gy) (Tables 1 and 2 and Appendix Table 1). One trial used a proton therapy boost after initial photon therapy (13, 14, 59). All studies reported that higher-dose EBRT was associated with increased rates of freedom from biochemical failure at 5 to 10 years compared with lower-dose EBRT. No differences in urinary or bowel toxicities between higher- and lower-dose EBRT were found.

Four RCTs (5 publications [16–19, 71]) and 2 retrospective analyses (72, 73) compared standard fractionation with hypofractionation. No statistically significant differences in freedom from biochemical failure or urinary and bowel toxicities were found between groups. A retrospective study comparing doses of hypofractionated EBRT also did not find statistically significant differences in urinary or bowel toxicities during and after completion of treatment (74).

Intra-LDRBT Comparisons

One RCT (3 publications [20–22]) and 2 retrospective studies (3 publications [75–77]) examined LDRBT dose or radionuclide comparisons (Table 2 and Appendix Table 1). The RCT compared iodine-125 (144 Gy) with palladium-103 (125 Gy) and found little or no difference between groups in freedom from biochemical failure at 3 and 6 years and in urinary or bowel toxicities (20–22). The first retrospective study showed that a higher biological effective dose (>220 Gy) using either iodine-125 or palladium-103 improved the overall survival rate and the 5-year rate of freedom from biochemical failure compared with a lower dose (≤ 220 Gy) in patients at higher risk for progression of prostate cancer (75, 76), whereas the second retrospective study comparing high- versus low-dose LDRBT found no significant differences in bowel or urinary toxicities or erectile dysfunction between groups (77).

Strength of Evidence for the Comparisons

We rated the strength of the body of evidence for intra-EBRT comparisons as moderate (Appendix Table 3). We rated evidence for all of the other comparisons as insufficient.

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Appendix Table 3. Strength of Evidence for Radiation Treatments of Clinically Localized Prostate Cancer  [Web-Only](#)**Discussion**

This updated review showed unclear effectiveness of radiation treatments compared with no treatment or no initial treatment of localized prostate cancer on patient survival. Similarly, evidence was insufficient to determine whether certain forms of radiation treatment were more effective than others. Retrospective data suggested that radiation treatments were associated with increased urinary or bowel problems compared with no treatment or no initial treatment. Studies suggested that brachytherapy might be associated with more urinary toxicity than EBRT. For dose comparisons, moderate-strength evidence showed that higher EBRT doses were associated with increased rates of long-term biochemical control than were lower EBRT doses.

Summarizing and interpreting this body of evidence was challenging for several reasons. First, cross-study comparisons were difficult because studies inconsistently defined and reported many of the outcomes of interest. Second, most of the evidence came from observational studies in which patients probably had treatments tailored to their individual risk profiles. For instance, low-risk patients may have been selectively treated with brachytherapy, whereas intermediate-risk patients may have been treated with EBRT. Comparative treatment efficacies are difficult to determine from such selection biases (notably, even among patients with T1 or T2 prostate cancer, the underlying risk for progression of prostate cancer varies widely, because this risk is also dependent on the Gleason score, pretreatment PSA concentration, and other factors). Third, while our focus was clinically localized prostate cancer (stages T1 and T2), approximately one third of the studies reviewed included up to 20% of patients with stage T3 or higher disease. Similarly, approximately one half of the studies had some patients who received ADT. Many of these studies did not report results stratified by tumor stage or ADT use.

An RCT not included in our review that compared radiation therapy plus concurrent ADT with ADT alone in patients with predominately stage T3 prostate cancer reported a survival benefit for the concurrent radiation therapy group (78). Although these results indirectly suggest a beneficial effect of radiation therapy over no initial treatment, a direct comparative study in appropriately selected patients with clinically localized prostate cancer is needed to either confirm or refute this conjecture. Two ongoing RCTs are comparing active surveillance with radical prostatectomy and radiation therapy: the Canadian START (A Phase III Study of Active Surveillance Therapy Against Radical Treatment in Patients Diagnosed With Favourable Risk Prostate Cancer) trial (ClinicalTrials.gov identification number: [NCT00499174](#)) and the British ProtecT (Prostate Testing for Cancer and Treatment) trial (ClinicalTrials.gov identification number: [NCT00632983](#)). Results from these trials should help clarify which men can be safely observed and which men need therapy and how radiation therapy and radical prostatectomy compare as the primary treatment approach. Much research remains to be done to evaluate EBRT versus brachytherapy and the various dose and fractionation schedules.

In summary, currently available evidence is insufficient to draw definitive conclusions about the effectiveness of radiation treatments for localized prostate cancer compared with no treatment or no initial treatment. Despite the addition of new studies, these conclusions remain largely similar to those from the 2008 review (4).

Article and Author Information

Disclaimer: The authors of this report are responsible for its content. Statements in the report should not be constituted as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

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