Technology Assessment

Technology Assessment Program

Comparative evaluation of radiation treatments for clinically localized prostate cancer: an update

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Radiation Therapy for Localized Prostate Cancer: an Update

Technology Assessment Report

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The investigator, Tomas Dvorak, M.D. discloses his affiliation as a Communications Committee Member for the American Society for Radiation Oncology. This is a voluntary position. Dr. Dvorak does not receive any financial remuneration from participating on this committee.

All other investigators do not have any affiliation or financial involvement related to the materials presented in this report.

Peer Reviewers

We wish to acknowledge individuals listed below for their review of this report. This report has been reviewed in draft form by individuals chosen for their expertise and diverse perspectives. The purpose of the review was to provide candid, objective, and critical comments for consideration by the EPC in preparation of the final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers.

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Abbreviations

2D-RT	conventional (non-3D planned) RT
3D-CRT	conformal RT
ADT	androgen deprivation therapy
AUA	American Urological Association
bDFS	biochemical (PSA) disease free survival
BED	biological effective dose
bNED	Biochemical no evidence of disease; same as bDFS
BT	Brachytherapy
CRT-PO	conformal RT prostate only
EBRT	external beam RT (including 2D-RT, 3D-CRT, IMRT)
FFBF	freedom from biochemical failure
Gy	Gray (unit of radiation dose)
GyE	Gray equivalents (used for particle therapy dose reporting)
HDR or HDRBT	high dose rate brachytherapy
IGRT	image guided RT (including IMRT and SBRT)
IMRT	intensity modulated RT
LDR or LDRBT	low dose rate brachytherapy
nADT	Neo-adjuvant androgen deprivation therapy
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NT	No treatment or no initial treatment
PSA	Prostate-specific antigen
PT	proton or particle therapy
QoL	quality of life
PPI	Permanent Prostate Implant Brachytherapy
RT	radiation therapy
RTOG	Radiation Therapy Oncology Group
SBRT	stereotactic body RT
SEER	Surveillance, Epidemiology, and End Results Program of the NCI
TURP	transurethral resection of the prostate
WW	watchful waiting

Executive Summary

Background

The Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested this report from The Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the following Evidence-based Practice Center: Tufts EPC (Contract No. 290 2007 10055 I).

Prostate cancer is the most common noncutaneous malignancy diagnosed in men in the United States. The vast majority of patients diagnosed today have clinically localized prostate cancer (T1-T2N0), which is the subject of this report. A Comparative Effectiveness Review of Therapies for Clinically Localized Prostate Cancer was undertaken on behalf of the Agency for Healthcare Research and Quality (AHRQ) by the Minnesota Evidence-based Practice Center (EPC) in 2007 (Wilt et al. Comparative effectiveness of therapies for clinically localized prostate cancer. Comparative Effectiveness Review No. 13, prepared by Minnesota Evidence-based Practice Center under contract no. 290-02-0009 Rockville, MD: Agency for Healthcare Research and Quality, February 2008. Available at effectivehealthcare.ahrq.gov/reports/final.cfm). The report concluded that "No one therapy can be considered the preferred treatment for localized prostate cancer due to limitations in the body of evidence as well as the likely tradeoffs an individual patient must make between estimated treatment effectiveness, necessity, and adverse effects. All treatment options result in adverse effects (primarily urinary, bowel, and sexual), although the severity and frequency may vary between treatments. Even if differences in therapeutic effectiveness exist, differences in adverse effects, convenience, and costs are likely to be important factors in individual patient decision making." As more studies on radiation treatments have been published since the Minnesota report, the Centers for Medicare and Medicaid Services (CMS) is interested in an update. After consultation with AHRQ and CMS, this technology assessment has been commissioned specifically to examine the recent comparative studies on radiation treatments of clinically localized prostate cancer.

Methods

This report addressed the following key questions:

1. What are the benefits and harms of radiation therapy for clinically localized prostate cancer compared to no treatment or no initial treatment (watchful waiting, active surveillance, or observation) in terms of clinical outcomes?
2. What are the benefits and harms of different forms of radiation therapy for clinically localized prostate cancer in terms of clinical outcomes? The comparisons of interest are between the following radiation modalities: stereotactic body radiation therapy (SBRT, including CyberKnife® therapy), classically fractionated external beam radiation therapy (EBRT, including 3D-conformal radiation therapy, intensity modulated radiation therapy, and particle therapy), high dose rate brachytherapy (HDRBT), and low dose rate brachytherapy (LDRBT, including permanent brachytherapy).
3. How do specific patient characteristics, e.g., age, race/ethnicity, presence or absence of comorbidities, preferences (e.g., tradeoff of treatment-related adverse effects vs. potential for disease progression) affect the outcomes of these different forms of radiation therapy?

We relied on findings from the 2008 comparative effectiveness review of therapies for clinically localized prostate cancer conducted by the Minnesota EPC as a springboard for our review. As the Minnesota review conducted its literature search through mid-September 2007, we conducted our literature search from January 2007 to ensure that all relevant and eligible studies are included. The methods for this technology assessment largely follows the methods suggested in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews, Version 1.0 published by AHRQ (available at effectiveheealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf).

We included randomized controlled trials and non-randomized direct comparative studies of men with clinically localized disease that reported clinical outcomes for T1 or T2 disease. We excluded single cohort studies, adjuvant, salvage, or post-prostatectomy radiation therapy studies, and studies evaluating androgen deprivation therapy. The intervention of interest was radiation treatment used as a first line treatment of prostate cancer. The treatments included various forms of external beam radiation therapy (intensity-modulated radiotherapy, conformal radiation, stereotactic body radiation including CyberKnife®, and proton beam), and brachytherapy (permanent seed implantation and high dose rate temporary brachytherapy). The treatments reviewed also included combination radiation therapies, such as external beam radiation therapy with brachytherapy boost. The comparators of interest were no treatment or no initial treatment (including watchful waiting and active surveillance) and alternate forms of radiation therapy. Outcomes of interest included overall and prostate cancer-specific survival, metastatic and/or clinical progression free survival, freedom from biochemical (PSA) failure, quality of life, bowel and urinary toxicities, and sexual dysfunction.

From the included studies, we extracted information on patient samples, radiation treatment characteristics (e.g., type of radiation (proton vs. photon), source of radiation (linear accelerator, Cobalt-60, internally planted radioactive seeds), dose, number of fractions, and manufacturer of device), treatment planning algorithm, outcomes (clinical and biochemical), adverse events, and study design. We used a 3-grade (A, B, C) rating system to rate the quality of the individual study. We also used a 3-category rating system (high, moderate, insufficient) to assess the overall strength of evidence for the outcomes reported in each of the comparisons.

Results and Strength of Evidence

We searched for articles on radiation treatments for prostate cancer published between January 2007 and December 2009 in the MEDLINE® and Cochrane Central database and found 51 out of 1,283 articles that met our inclusion criteria. We also added 9 randomized controlled trials (RCTs) relevant to radiation treatments identified in the Minnesota report to our analysis. A total of 62 articles were included in our review. The table below summarized the strength of evidence for the outcomes reported in each of the comparisons.

Table 1. Strength of evidence for radiation treatments of clinically localized prostate cancer

	High	Moderate	Insufficient
KQ1. Radiation therapy versus no treatment or no initial treatment			
Freedom from Biochemical failure			X[a]
Disease Specific Survival			X[b]
Genitourinary/Gastrointestinal Toxicity			X[c]
KQ 2. Different forms or doses of radiation			
SBRT versus EBRT			X[a]
SBRT versus HDRBT			X[a]
SBRT versus LDRBT			X[a]
EBRT versus HDRBT			X[a]
EBRT versus LDRBT			
Freedom from Biochemical failure			X[b]
Disease Specific Survival			X[c]
Genitourinary/Gastrointestinal Toxicity			X[b]
LDRBT versus HDRBT			
Freedom from Biochemical failure			X[c]
Disease Specific Survival			X[c]
Genitourinary/Gastrointestinal Toxicity			X[c]
Combined RT modality comparisons			
Freedom from Biochemical failure			X[c]
Genitourinary/Gastrointestinal Toxicity			X[d]
Intra SBRT comparisons			
Freedom from Biochemical failure			X[c]
Genitourinary/Gastrointestinal Toxicity			X[c]
Intra EBRT comparisons			
Freedom from Biochemical failure		X[e]	
Genitourinary/Gastrointestinal Toxicity		X[e]	
Intra BT comparisons			
Freedom from Biochemical failure			X[f]
Genitourinary/Gastrointestinal Toxicity			X[b]
KQ 3. Patient characteristics related to radiation treatment outcomes			
Baseline risk (Stage, PSA, Gleason score)			X[b]
Gleason score/PSA levels			X[c]

a: No study available

b: Results inconsistent across studies

c: Only one study

d: Predominantly C quality studies

e: ≥2 B quality RCTs that reported similar results (significant difference or no difference)

f: Only one RCT and one retrospective study

Key Question 1. What are the benefits and harms of radiation therapy for clinically localized prostate cancer compared to no treatment or no initial treatment (watchful waiting, active surveillance, or observation) in terms of clinical outcomes?

The strength of evidence for comparing radiation therapy with no treatment or no initial treatment was rated "insufficient" because available data were all provided by retrospective analyses. The Minnesota review did not identify any RCTs that compared external beam radiation therapy with no treatment or no initial treatment; neither did this update review. Data from three retrospective cohorts showed mostly non-significant improvement in disease-specific patient survival in those who received radiation therapy compared to those who had either no treatment or no initial treatment.

Key Question 2. What are the benefits and harms of different forms of radiation therapy for clinically localized prostate cancer in terms of clinical outcomes? The comparisons of interest are between the following radiation modalities: stereotactic body radiation therapy (SBRT,), classically fractionated external beam radiation therapy (EBRT, including 3D-conformal radiation therapy, intensity modulated radiation therapy, and particle therapy), high dose rate brachytherapy (HDRBT), and low dose rate brachytherapy (LDRBT, including permanent brachytherapy).

There were no comparisons between SBRT and any other radiation modality. There were also no comparisons between EBRT and HDRBT.

LDRBT vs. EBRT

Evidence for the comparative efficacy between LDRBT and EBRT on patient survival was rated "insufficient" as there was only one eligible study in this comparison. This retrospective study suggests that there was no difference in disease specific patient survival comparing LDRBT with EBRT.

Evidence for the comparative efficacy between BT and EBRT on biochemical control was rated "insufficient" because the results were inconsistent across the four B-rated studies in this comparison. While two studies found better biochemical control in the LDRBT group compared to the EBRT group, two studies did not find differences between groups.

Evidence for the comparative efficacy between LDRBT and EBRT for genitourinary and gastrointestinal toxicities was rated "insufficient" because the four B-rated studies did not report consistent results. Two studies did and two studies did not show that LDRBT was associated with significantly more genitourinary toxicity than EBRT. For gastrointestinal toxicity, one study showed that LDRBT was associated with less gastrointestinal toxicity compared with EBRT, the other three studies did not find significant difference between LDRBT and EBRT.

Regarding sexual dysfunction, one study showed significantly better outcomes with LDRBT compared with EBRT, another study also reported better outcomes with LDRBT compared with EBRT but the P value of this study was not reported..

Only one study reported cancer incidence comparing LDRBT with EBRT; this study showed a significantly lower incidence of bladder and rectal cancer with LDRBT compared with EBRT.

LDRBT vs. HDRBT

Evidence for the comparative efficacy between HDRBT and LDRBT on biochemical outcome was rated "insufficient" as only one retrospective study provided relevant data.

Comparing HDRBT using Ir-192 (38 Gy or 42 Gy) with LDRBT using Pd-103 (120 Gy), this study did not find a difference in the 5-year freedom from biochemical failure in the two groups.

Combination Therapies: LDRBT plus EBRT in different doses

Evidence on the comparative efficacy of different combinations of radiation was rated "insufficient", as there were only a few studies in each of the comparisons.

One study did not find a difference in biochemical failure comparing LDRBT plus EBRT in different doses, while another study did not find a difference in biochemical failure comparing LDRBT plus EBRT versus LDRBT. One study did not find a difference in biochemical or clinical failure comparing EBRT with EBRT plus HDRBT.

Limited data suggest greater genitourinary toxicity in EBRT plus LDRBT versus EBRT, and BT plus EBRT versus EBRT.

Our analysis of the data from a study comparing EBRT plus BT versus EBRT showed a significantly increased rate of second primary cancers and late second primary cancers (≥ 5 years) in the EBRT arm.

In addition to comparing different modalities of radiation therapy with each other, we also reviewed comparative evidence within a given radiation modality.

Intra-SBRT comparisons

Evidence for the comparative efficacy on SBRT was rated "insufficient" as only one study qualified for inclusion in this review. This retrospective study found little difference in bladder and rectal toxicities between those who received 35 Gy in 5 fractions and those who received 36.25 Gy also in 5 fractions.

Intra-EBRT Comparisons

For EBRT dose comparison, "moderate" level of evidence from eight studies suggests that higher dose EBRT is associated with increased rates of freedom from biochemical failure at 5 to 10 years compared to lower dose EBRT.

Data from five studies suggest that there is little or no difference in acute and late genitourinary or gastrointestinal toxicities between higher and lower dose EBRT.

For EBRT fractionation comparison, data from three studies suggest that there is no difference between standard fractionation and hypofractionation arms as tested in the studies for freedom from biochemical failure. There is also little or no difference in gastrointestinal toxicity between arms. One B-rated RCT reported a slightly higher acute genitourinary toxicity in the hypofractionation arm compared with the standard fractionation arm, but there was no difference in late genitourinary toxicity.

Intra-LDRBT comparisons

For LDRBT dose and radionuclide comparison studies, "insufficient" level of evidence from one RCT suggests there is little or no difference between I-125 (144 Gy) and Pd-103 (125 Gy) in terms of freedom from biochemical failure at 3 to 6 years. One analysis found that higher biological effective dose (BED) (>220 Gy) using either I-125 or Pd-103 may improve the 5-year rate of freedom from biochemical failure compared with lower dose (≤220 Gy) in those with higher risk of prostate cancer progression (Gleason score 8 to 10).

Key Question 3. How do specific patient characteristics, e.g., age, race/ethnicity, presence or absence of comorbidities, preferences (e.g., tradeoff of treatment-related adverse effects vs. potential for disease progression) affect the outcomes of these different forms of radiation therapy?

There were few studies on the potential effects of different patient characteristics on treatment outcomes, apart from patients' baseline risk. The strength of evidence for evaluating baseline risk as a modifier of outcomes of radiation therapies was rated "insufficient" because there were limited studies for the comparisons reviewed.

Discussion

Because prostate cancer tends to have a long clinical course typically measured in decades, many studies focused on short term adverse events or biochemical control rather than long term clinical efficacy outcomes like metastases and disease-specific mortality. It should be noted that in the studies reviewed, the event rates for grade 3 or greater urinary or bowel toxicity are so low that any statistically significant differences between treatment arms may not translate into substantive clinical differences.

Many of the findings reported in this review were inconsistent for each of the outcomes of interest. The studies reviewed showed substantial heterogeneity. Even among patients with T1 or T2 prostate cancer, the underlying risk of prostate cancer progression varies widely. An important weakness in many of these comparative analyses is that patients were given treatments tailored to their individual risk profile (e.g., patients with low risk prostate cancer tend to be given BT versus those with intermediate risk prostate cancer tend to be given EBRT); this makes it difficult, if not impossible, to assess the comparative efficacies between two forms of radiation treatments as the underlying risk of prostate cancer progression in the two groups of patients may be fundamentally different.

The focus of this review is clinically localized prostate cancer (stages T1 and T2). The majority of the patients in these studies had clinically localized disease (stage T1 and T2); however, approximately one-third of the studies reviewed included up to 20% of patients with stage T3 or higher disease. Excluding them would lead to a drastically reduced number of qualified studies and may inadvertently discard useful data. Similarly, approximately half of the studies had some patients who received androgen deprivation therapies (ADTs), either as a neoadjuvant, concurrent or adjuvant therapy. Many of the studies that included patients with stage T3 or higher disease or ADTs did not report results stratified by patients' tumor stage or ADT use. Therefore, we are not always able to draw conclusions on the specific treatment effects of the different forms of radiation alone for clinically localized prostate cancer patients (stage T1 and T2), without contamination of results from patients with stage T3 or higher disease, or without contamination of results from patients also treated with ADTs. How these contaminations would affect the "true" treatment effect estimate of radiation alone in only T1-T2 disease is unpredictable.

Conclusion

Definitive benefits of radiation treatments compared to no treatment or no initial treatment for localized prostate cancer could not be determined because available data were insufficient. Data on comparative effectiveness between different forms of radiation treatments

(BT, EBRT, SBRT) are also inconclusive whether one form of radiation therapy is superior to another form in terms of overall or disease-specific survival. Studies suggest that higher EBRT dose results in increased rates of long-term biochemical control than lower EBRT dose. EBRT administered as a standard fractionation or moderate hypofractionation does not appear to differ with respect to biochemical control and late genitourinary and gastrointestinal toxicities. Available data suggest that BT might be associated with an increase in genitourinary toxicity compared with EBRT. BT appears to be largely comparable to EBRT in the rates of gastrointestinal toxicity. However, more and better quality studies are needed to either confirm or refute these suggested findings.

Introduction

The Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested this report from The Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the following Evidence-based Practice Center: Tufts EPC (Contract No. 290 2007 10055 I).

Prostate cancer is the most common noncutaneous malignancy diagnosed in men in United States. The American Cancer Society estimates that in 2009, approximately 192,000 men were diagnosed with prostate cancer, accounting for 25% of all new cancer cases, and that approximately 27,000 men died of the disease.[1] Median age at diagnosis is 67 years (seer.cancer.gov/csr/1975_2006/results_single/sect_01_table.11_2pgs.pdf). However, autopsy studies suggest that 30% of men already have undiagnosed prostate cancer by age 40 and as many as 70-80% may have clinically "silent" prostate cancer by age 85.[2] It has been estimated that approximately 50% of men undergo a routine prostate specific antigen (PSA) screening. Widespread PSA testing has doubled the incidence of prostate cancer, and results in the lifetime risk of prostate cancer of approximately 16% (seer.cancer.gov/statfacts/html/prost.html).

In addition to increasing incidence, PSA screening is also changing the characteristics of diagnosed prostate cancer. Data from the CaPSURE registry containing 8,685 men with biopsy-proven prostate cancer showed that the incidence of clinically "silent" T1 tumors (tumors diagnosed incidentally during transurethral resection of prostate for benign prostatic hypertrophy or tumors diagnosed by PSA screening, without clinical evidence by digital rectal exam) increased from 17% in 1989 to 48% in 2001.[3] In the Prostate, Lung, Colorectal, and Ovarian Screening Trial (PLCO), 95% of patients were diagnosed with clinically localized disease, while only 1.6% were diagnosed with locally advanced disease, and 2.4% were diagnosed with metastatic disease.[4] Overall, the vast majority of patients diagnosed today have clinically localized prostate cancer (T1-T2N0), which is the subject of this report.

To appreciate the impact of treatment interventions, it is important to understand the natural history of untreated clinically localized prostate cancer. Our understanding of this process is limited because of the stage shift to earlier disease with PSA screening discussed above. Investigators from a European prostate cancer screening trial (ERSPC) have estimated that the mean lead time bias for screening-detected cancers versus clinically-detected cancers could be 11.2 years, with an estimated overdetection rate of 50%.[5] This suggests that after PSA diagnosis of prostate cancer (Stage T1c), it can take more than 10 years before the disease becomes clinically apparent. The natural history of prostate cancer diagnosed clinically is better characterized based on data from pre-PSA era. A cohort study from Sweden tracked 223 patients with localized prostate cancer diagnosed between 1977 and 1984, with a median follow-up of 21 years.[6] Most of the cancers had an indolent course during the first 15 years of follow-up, with progression-free survival of 45%, distant metastasis-free survival of 77%, and prostate cancer-specific survival of 79%. However, between 15 and 20 years of follow-up, there was a significant decrease in progression-free survival to 36%, distant metastasis-free survival to 51%, and prostate cancer-specific survival of 54%. The authors concluded that most prostate cancer patients diagnosed clinically at an early stage have an indolent course, but aggressive metastatic disease may develop in the long term. A similar cohort study from Connecticut tracked 767 patients with localized prostate cancer diagnosed between 1971 and 1984.[7] Their 20-year prostate cancer-specific survival was 71% and overall survival was 7%. The 20-year cancer-specific

survival for patients with a low grade (Gleason Score 2-6) was 81%, with intermediate grade (Gleason Score 7) was 55%, and with high grade (Gleason Score 8-10) was 34%. In contrast to the Swedish study, there was no worsening of cancer-specific survival after 15 years. Extrapolating from these studies, the natural history for an average 70 year old patient diagnosed today could result in the development of clinically evident disease in 10 years and a 50% chance of survival from prostate cancer in 30 years after diagnosis, though the rate would be dependent on initial grade of the tumor. To put these numbers into perspective, for that average 70 year old man the probability of survival for 10 years (when he would develop clinically evident disease) is 65% and the probability of survival for another 30 years (when he would have a 50% risk of dying from prostate cancer) is less than 1% (ssa.gov/OACT/STATS/table4c6.html).

Because of the differential survival rates based on tumor grade, there has been an increased focus on identifying and treating patients with aggressive subtypes whose overall survival is likely to be impacted by their cancer, while deferring treatment for patients with indolent subtypes and/or short life-expectancy, whose overall survival is not likely to be impacted by their cancer. Depending on patient's risk profile, there are numerous treatment options available, which include active surveillance (deferred initial therapy; with continued surveillance and predetermined action levels that will trigger definitive therapy), watchful waiting (either the same as active surveillance or as no definitive therapy regardless of disease progression, until death), surgery, radiation therapy, cryotherapy, high intensity focused ultrasound, and androgen deprivation therapy. For the purpose of this report, watchful waiting is considered equivalent to active surveillance, and the No Treatment or No Initial Treatment comparator category in Key Question 1 (see below) includes active surveillance, watchful waiting, and observation. Currently, the National Comprehensive Care Network guidelines represent a standard of care in United States, and the NCCN prostate cancer guideline outlines which treatment options may be appropriate for which patients (nccn.org/professionals/physician_gls/PDF/prostate.pdf).

A Comparative Effectiveness Review of Therapies for Clinically Localized Prostate Cancer was undertaken on behalf of the Agency for Healthcare Research and Quality (AHRQ) by the Minnesota Evidence-based Practice Center (EPC) in 2007 (Wilt et al. Comparative effectiveness of therapies for clinically localized prostate cancer. Comparative Effectiveness Review No. 13, prepared by Minnesota Evidence-based Practice Center under contract no. 290-02-0009 Rockville, MD: Agency for Healthcare Research and Quality, February 2008. Available at effectivehealthcare.ahrq.gov/reports/final.cfm). The report concluded that "No one therapy can be considered the preferred treatment for localized prostate cancer due to limitations in the body of evidence as well as the likely tradeoffs an individual patient must make between estimated treatment effectiveness, necessity, and adverse effects. All treatment options result in adverse effects (primarily urinary, bowel, and sexual), although the severity and frequency may vary between treatments. Even if differences in therapeutic effectiveness exist, differences in adverse effects, convenience, and costs are likely to be important factors in individual patient decision making." As more studies on radiation treatments have been published since the Minnesota report, the Centers for Medicare and Medicaid Services (CMS) is interested in an update. After consultation with AHRQ and CMS, this technology assessment has been commissioned specifically to examine the recent comparative studies on radiation treatments of prostate cancer.

Radiation therapy uses high-energy ionizing radiation to damage DNA of tumor cells, ultimately causing cell death and resulting in tumor eradication. As part of the radiation treatment, surrounding normal tissues are also irradiated, resulting in death of normal cells, and

leading to development of side effects. There are three fundamental questions involved with the delivery of radiation to a tumor: 1) What should be the actual target of radiation? 2) How do we deliver radiation to it most effectively and safely? 3) What dose scheme will we use? Understanding these questions will help to understand the evolution of radiation technology and current efforts at further advances.

From a technology perspective, there are multiple methods of delivering radiation to the prostate, and these are summarized in Figure 1. Radiation can be delivered from outside the body using man-made accelerators, which is known as teletherapy or external beam radiation therapy (EBRT). Or it can be delivered by implanting naturally radioactive elements directly into the tumor, which is known as brachytherapy (BT). The process of planning a treatment and delivering radiation therapy is different, depending on whether EBRT or BT is used. For EBRT, the first step involves acquiring a planning CT scan of the patient to outline the tumor. The next step is to virtually plan the treatment using computer models to ensure that radiation is delivered safely and effectively. Finally, the patient comes for the treatment itself, which is typically delivered in multiple sessions called fractions. For BT, treatment planning can be done either prior to the surgical implant in a similar fashion as for EBRT or it can be done inside the operating room at the time of the implant of radioactive sources, usually using ultrasound guidance.

Actual target of radiation

The extent of the irradiation area (field size) is an important issue, because the larger the area treated, the more normal tissues are incidentally irradiated, and the more frequent and severe the side effects (conversely, the smaller the field size, the more likely that the entire tumor will not be adequately treated). Field size is driven both by clinical decisions about the extent of disease, as well as by technical factors regarding prostate visualization and prostate motion. Many technological advances in radiation therapy focus on minimizing the treated volume to minimize toxicity. Prostate cancer typically arises in multiple foci within the prostate gland, and thus far no imaging methods have been able to reliably identify involved areas of the prostate. For now, the entire prostate gland typically serves as the target for radiation. For some prostate tumors, there can be subclinical microscopic extension outside of the prostate into the surrounding tissues, seminal vesicles, and regional lymph nodes. There is no definitive evidence available to guide radiation oncologists on when to treat just the prostate gland, when to irradiate some of the surrounding tissues, when to irradiate the seminal vesicles, and when to treat the lymph nodes. First efforts at targeting the prostate used plain x-rays for visualization. Unfortunately, the prostate gland cannot be reliably distinguished from the surrounding soft tissues on plain films. This method of treatment planning is called two-dimensional planning. Development of CT scans for treatment planning in the 1980's resulted in better visualization of the prostate gland and the lymphatic drainage. The ability to outline the target in three dimensions led to 3D planning, which is the standard today. However, there is a wide variability among individual radiation oncologists in outlining the shape and location of the prostate gland or the lymphatic drainage.[8, 9] MRI scans are able to better distinguish the soft tissue densities of the prostate and peri-prostatic tissue, and are becoming a more common tool for radiation oncologists to delineate the radiation target.

Another factor complicating the determination of tumor location is the fact that the planning CT scan is a momentary snapshot in time that shows only where the prostate gland happens to be during the scan. From day to day (inter-fraction motion), and even from minute to minute during

treatment (intra-fraction motion), the prostate can move significantly.[10] The location of the prostate is determined by a number of factors, including the volume of rectal filling and the amount of bladder filling. If we do not know where the prostate may be at any given moment, we need to treat the entire area where it could potentially be, and thus irradiate unnecessarily significant amount of normal tissues. There are three broad strategies to deal with the motion of the prostate: 1) improved immobilization of the prostate, 2) increased frequency of localizing (imaging) the prostate over time, 3) implanting radiation directly into the prostate, such that the sources move with the prostate.

There are a number of immobilization techniques or devices employed during external beam radiation therapy, such as abdominal compression, endorectal balloon, foot holders, knee supports, and pelvic immobilizers, which attempt to more reproducibly fix the position of the prostate. In terms of prostate localization for treatment, patients used to be positioned on the treatment table every day using external skin tattoos, and their position would be verified once per week using bony landmarks on x-ray. Advancements in localization have included using daily imaging prior to each treatment session with ultrasound, x-rays combined with implanted fiduciary markers, and on-board CT scans. This approach eliminates daily (inter-fraction) variability in prostate position resulting from bladder and rectal filling. However, there is still the issue of intra-fraction mobility during the treatment itself. Two approaches are currently used to address this problem: implanted fiducial markers into the prostate that are tracked continuously during the treatment using electromagnetic fields (Calypso System from Calypso Medical Technologies), or implanted fiducial markers that are tracked prior to each treatment beam every few seconds (CyberKnife® from Accuray Inc., Sunnyvale, CA).

Implanting radiation directly into the target is another method of improving dose delivery. There are two forms: 1) permanent implantation of many radioactive seeds into the prostate, which will deliver their radiation dose over the course of weeks to months, and is known as low dose rate brachytherapy (LDRBT), and 2) temporary implantation of catheters into the prostate, through which radioactive seeds are temporarily placed and deliver their radiation dose over the course of minutes, and is known as high dose rate brachytherapy (HDRBT). The downside of this approach is that it is an operative procedure and that radiation can only be delivered to the prostate, and not easily to seminal vesicles or lymph nodes.

Delivering radiation effectively and safely

Planning the radiation treatment involves generating a virtual model of the patient and mathematically estimating the dose that the tumor and the surrounding normal tissues will receive during treatment. The dose to each individual patient is actually not known; the estimated dose is verified by irradiating a physical model or an x-ray film and measuring the delivered dose. There are several different models of radiation deposition available. Initially, plain x-rays were used for treatment planning, and the amount of dose given was only calculated for few points within the patient. Using this approach, the amount of radiation actually received by the various parts of the prostate and by the surrounding normal organs was essentially unknown. This process is known as conventional radiation or 2D-radiation. When CT scans became incorporated into the treatment planning process, the prostate gland as well as the surrounding organs could be individually identified. The treatment planning software allowed the calculation of dose at any point in the 3-D space, allowing for a much more precise estimate of dose to the target and to surrounding normal organs. In addition, radiation could be targeted more tightly around the prostate to decrease irradiation of surrounding normal tissues. This process is known

as 3D-conformal radiation (3D-CRT). The next improvement came with the ability to change the intensity of the radiation beam itself, while the radiation was being delivered. This process is known as intensity modulated radiation therapy (IMRT), and allows much more precise control over where the radiation is deposited. As discussed in the prostate localization section, incorporation of daily pre-treatment imaging allowed further precision in targeting the radiation, and is known as image-guided radiation therapy (IGRT). IMRT and IGRT are typically used together, such that the position of the beam is adjusted prior to every treatment (IGRT), and the radiation intensity of the beam is modulated once the treatment begins (IMRT). Further incorporation of various body immobilization systems into IMRT with IGRT, together with increased daily dose, and limiting the number of treatments to one or few, is known as stereotactic body radiation therapy (SBRT)[11]. An alternative means of delivering radiation therapy using external beam to the prostate involves proton therapy, using exactly the same process as the standard photon EBRT, but using proton particles instead. Despite the technical advances in delivery of external beam radiation, it may not possible to deliver sufficiently high dose without incurring unacceptable normal tissue toxicity. In these instances, efforts are under way to combine EBRT with brachytherapy for dose escalation, either as EBRT + HDRBT or EBRT + LDRBT (Table 1).

Dose schema used in radiation delivery

The unit of absorbed radiation dose is Gray (Gy), which corresponds to absorption of one joule of energy by one kilogram of matter. Historically, dose in prostate cancer was delivered in 1.8 – 2.0 Gy per treatment (fraction). Before development of 3D-CRT (see above), maximum tolerable dose was approximately 70 Gy delivered in 35 fractions over 7 weeks, above which unacceptable toxicity resulted. With technology developments described above, dose escalation over 80 Gy has been employed. Current NCCN guidelines recommend 75.6 to 80+ Gy doses, delivered over 7-8 weeks. There is some evidence that prostate cancer may be better treated with larger doses per fraction (> 2 Gy) than is currently standard.[12] To account for the fact that a larger dose per fraction results in dramatically more DNA damage and subsequently cell kill, it is important to convert the physical dose to biologically-equivalent dose (BED).[13] Using this concept, a regimen of 7 Gy per fraction for 5 treatments (absolute dose 35 Gy) could result in biologically equivalent tumor control to an IMRT regimen of 2 Gy per fraction for 42 fractions (absolute dose 84 Gy); absolute dose comparisons between different regimens may not be meaningful if the dose per fraction is not the same.

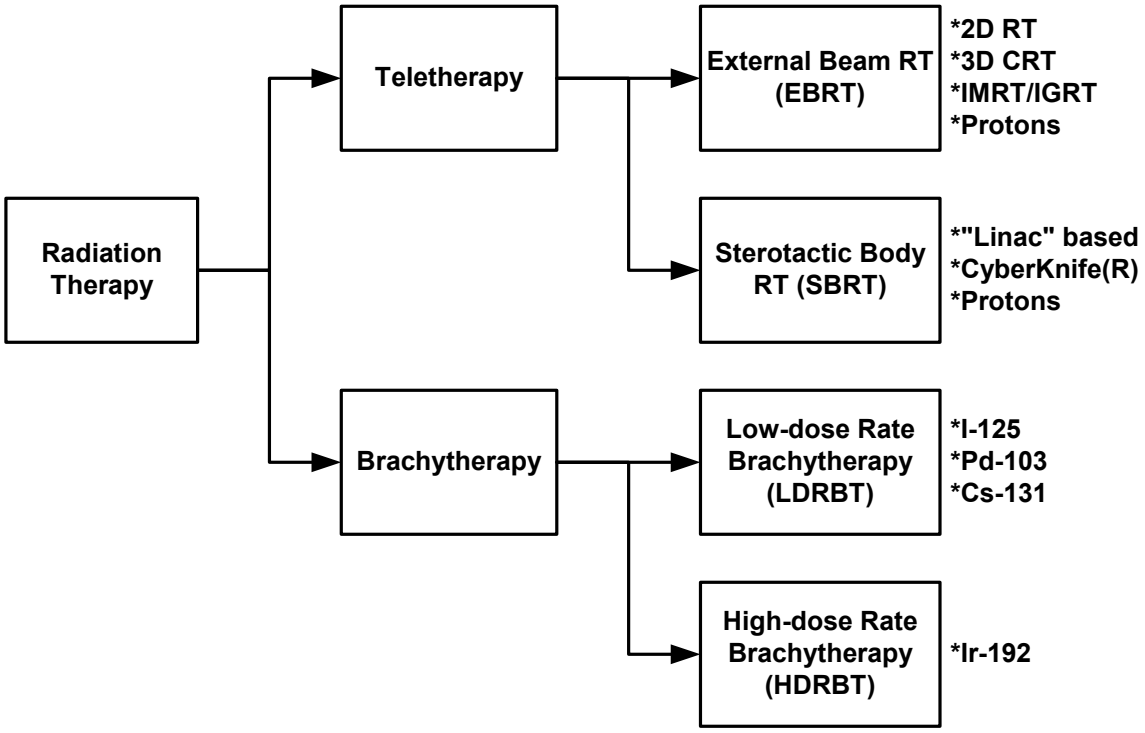
Key questions for this report

Understanding the process of delivering radiation therapy described above is crucial to comprehend this technology assessment. This report addressed the following key questions:
1. What are the benefits and harms of radiation therapy for clinically localized prostate cancer compared to no treatment or no initial treatment (watchful waiting, active surveillance, or observation) in terms of clinical outcomes?
2. What are the benefits and harms of different forms of radiation therapy for clinically localized prostate cancer in terms of clinical outcomes? The comparisons of interest are between the following radiation modalities: stereotactic body radiation therapy (SBRT, including CyberKnife® therapy), classically fractionated external beam radiation therapy (EBRT, including 3D-conformal radiation therapy, intensity modulated radiation therapy, and particle therapy), high dose rate brachytherapy (HDRBT), and low dose rate brachytherapy (LDRBT,

including permanent brachytherapy). These modalities will be specifically compared with each other, i.e., LDRBT VS. EBRT, HDRBT VS. LDRBT, SBRT vs. EBRT, SBRT vs. HDRBT, SBRT vs. LDRBT, EBRT vs. HDRBT, combination therapies, intra-SBRT comparisons, intra-EBRT comparisons, and intra-BT comparisons.

3. How do specific patient characteristics, e.g., age, race/ethnicity, presence or absence of comorbidities, preferences (e.g., tradeoff of treatment-related adverse effects vs. potential for disease progression) affect the outcomes of these different forms of radiation therapy?

Figure 1: Overview of radiation therapy modalities



2D RT is two-dimensional radiation therapy; 3D CRT is three dimensional conformal radiation therapy; IMRT is intensity modulated radiation therapy; IGRT is image-guided radiation therapy; I-125, Pd-103, Cs-131, and Ir-192 are radionuclides used in brachytherapy

Table 2: Comparison of external beam radiation therapy (EBRT) modalities

	CT Treatment Planning	Beam Intensity Modulation	Frequent Imaging	Stereotactic Immobilization	1-5 Treatment Fractions
2D RT					
3D CRT	X				
IMRT	X	X			
IGRT	X	X	X		
SBRT	X	X	X	X	X
Proton Therapy	X	+/-	X	X	+/-

Methods

The objective of this technology assessment is to assess, using a systematic review approach, the volume and type of evidence available on radiation treatment for localized prostate cancer. The purpose is to provide a basis for establishing how the research field is evolving and identify areas that may require further research. We relied on findings from the 2008 comparative effectiveness review of therapies for clinically localized prostate cancer conducted by the Minnesota EPC (Wilt et al. Comparative effectiveness of therapies for clinically localized prostate cancer. Comparative Effectiveness Review No. 13. (prepared by Minnesota Evidence-based Practice Center under contract no. 290-02-0009) Rockville, MD: Agency for Healthcare Research and Quality, February 2008, available at effectivehealthcare.ahrq.gov/reports/final.cfm) as a springboard for our review. As the Minnesota review conducted its literature search through mid-September 2007, we conducted our literature search from January 2007 to ensure that all relevant and eligible studies are included. The methods for this technology assessment largely follows the methods suggested in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews, Version 1.0 published by AHRQ (available at effectiveheealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf). Please note that explanations for abbreviations of frequently used technical terms have been repeated several times throughout the entire document to help clarify highly technical terminologies. See **Abbreviations** for a list of abbreviations used for the entire document.

Literature Search Strategy

Our search strategy used the National Library of Medicine's Medical Subject Headings (MeSH) keyword nomenclature developed for Medline® and adapted for use in other databases. The searches were limited to the English language. The texts of the major search strategies are given in Appendix A.

We searched the Medline and the Cochrane Library from January 2007 to December 2009 for studies involving adults with clinically localized prostate cancer who underwent radiation treatments. We combined search terms or MeSH terms for prostate neoplasm and terms relevant to radiation therapy (e.g., proton beam, particle beam, external beam, radiotherapy, intensity-modulated radiotherapy, brachytherapy). We limited the search to English language studies in adult humans. We included peer reviewed, primary studies of radiation treatment for clinically localized prostate cancer that had reported either clinical or biochemical outcomes. We excluded case reports and conference abstracts. We did not search systematically for unpublished data. Our local domain expert provided additional relevant and eligible citations.

The identified abstracts results were reviewed independently by six reviewers. All abstracts concerning technical aspects of radiation therapy were re-screened by a radiation oncologist.

Study Eligibility Criteria

Our three key questions concern mainly with radiation treatment. We focused only on direct comparative studies for this technology assessment. Because institutions sometime overhaul their radiation treatment in its entirety from one form to another form (e.g., switching from 3D-CRT to IMRT) and therefore direct comparative study between the different forms of treatment within the same institution would not be possible, we have relaxed this criterion to allow such studies as

long as the patients were consecutively enrolled. We assessed titles and/or abstracts of citations identified from our literature search for inclusion, using the criteria described below. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria. Results published only as abstracts were not included in our reviews because adequate information is not available to assess the validity of the data and these reports have generally not been peer-reviewed.

Study designs of interest

We included randomized controlled trials and non-randomized direct comparative studies (same institution, contemporaneous or consecutive enrollment is permissible) of men with clinically localized disease and reported clinical outcomes for T1 or T2 disease (no less than 80% T1 or T2 if the study reported a mixed population including T3 and T4).

We did not place sample size and follow-up length restrictions on these comparative studies.

We excluded single cohort studies, adjuvant, salvage, or post-prostatectomy radiation therapy studies, and studies evaluating androgen deprivation therapy in conjunction with radiation therapy.

Population and condition of interest

We included studies of men with clinically localized prostate cancer (T1-T2, N0-X, M0-X) regardless of age, histologic grade, PSA level, or whether they received hormonal treatments (provided the hormonal treatment was not a standard part of the overall treatment plan in one or both of the treatment arms). If the study did not clearly report T staging, we included the study only if it explicitly stated that it enrolled exclusively patients with localized or low risk disease.

Interventions of interest

The intervention of interest was radiation treatment. The radiation treatment had to be used as a first line treatment of prostate cancer. The treatments included external beam radiation therapy (conformal radiation, intensity-modulated radiotherapy, proton therapy) stereotactic body radiation, and brachytherapy (low dose rate permanent seed implantation and high dose rate temporary brachytherapy). We also included combination radiation therapies, such as external beam radiation therapy with brachytherapy boost. For studies that also examined watchful waiting, active surveillance, or observation, because the study investigators did not use consistent definitions for these terms (e.g., some defined watchful waiting as no definitive treatment ever and some defined it as definitive treatment if disease progresses), we accepted all the different definitions and considered all three to be equivalent and grouped all three into “no treatment or no initial treatment” group.

Comparators of interest

The comparators of interest were no treatment or no initial treatment (including watchful waiting and active surveillance) and alternate forms of radiation therapy.

Outcomes of interest

Outcomes of interest included overall survival, prostate cancer-specific survival, biochemical (PSA), metastatic and/or clinical progression free survival, health status, and quality of life. Adverse events included anticipated events such as bowel, bladder, and sexual dysfunction and unanticipated events.

Data Extraction

Data from each study were extracted by one of the reviewers and confirmed by another. The extracted data included information on patient samples, radiation treatment characteristics (e.g., type of radiation (proton vs. photon), source of radiation (linear accelerator, Cobalt-60, internally planted radioactive seeds), dose, number of fractions, and manufacturer of device), treatment planning algorithm, outcomes (clinical and biochemical), adverse events, and study design. For most outcomes, 6 months, 12 months, and/or only data from the last reported time point were included. We also evaluated potential sources of bias in the included studies with respect to adequate power, randomization, allocation concealment, intention to treat, adequate length of follow-up, number of dropouts and lost to follow-up. To minimize the possibility of between-EPC (Tufts and Minnesota) differences in interpretation of study findings, we elected to extract the data ourselves from those RCTs identified by the Minnesota report that were of relevance to this review.

Quality Assessment

We used predefined criteria to grade study quality as A, B, or C. This system defines a generic grading system that is applicable to varying study designs including RCTs, nonRCTs, and observational studies. For RCTs, we mainly considered the methods used for randomization, blinding, as well as the use of intention-to-treat analysis, the report of dropout rate and the extent to which valid primary outcomes were described and how well they were reported. For nonRCTs and observational studies, the following elements were considered in assessing quality: clear reporting of eligibility criteria, similarity of comparative groups in terms of baseline characteristics and prognostic factors, reporting on crossovers, differential loss to follow-up between the comparative groups or overall high loss to follow-up, adjustment for potential confounders, and validity and adequacy of the description of outcomes and results.

A (low risk of bias)

Studies rated "A" have the least bias and results are considered valid. These studies adhere mostly to the commonly held concepts of high quality including the following: a formal randomized controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20 percent dropout; clear reporting of dropouts; and no obvious bias.

B

Studies rated "B" are susceptible to some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category "A". The study may be missing information, making it difficult to assess limitations and potential problems.

C (high risk of bias)

Studies rated "C" have significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; there are large amounts of missing information, or major discrepancies in reporting.

Rating the Body of Evidence

We assigned an overall grade describing the strength of evidence for each key question that was based on the number and quality of individual studies, duration of follow-up and the consistency across studies. The grades corresponded to the following definitions:

High – **High confidence that the evidence reflects the true effect**. Further research is very unlikely to change our confidence in the estimate of effect. There is a high level of assurance with validity of the results for the key question based on at least two high quality studies with long-term follow-up of a relevant population. There is no important scientific disagreement across studies in the results for the key question.

Moderate – **Moderate confidence that the evidence reflects the true effect**. Further research may change our confidence in the estimates of effect and may change the estimate. There is a moderate level of assurance with validity of the results for the key question based on fewer than two high quality studies or in high quality studies that lack long-term outcomes of relevant populations. There is little disagreement across studies in the results for the key question.

Insufficient – Evidence is either unavailable or if available, a low level of assurance with validity of results for the key question. There could be disagreement across studies in the results for the key question.

The grades provide a shorthand notation of the strength of evidence supporting the answers to the key questions. However, they may oversimplify the many complex issues involved in appraising a body of evidence. The individual studies involved in formulating the composite grade differed in their design, reporting, and quality. As a result, the strengths and weaknesses of the individual reports addressing each key question would also be considered, as described in detail in the text and tables.

Data Synthesis

For key question 1 (radiation treatment vs. no treatment or no initial treatment) and key question 2 (comparing different forms of radiation treatment), eligible studies were compiled into sets of summary tables that succinctly present the study features including design, patient-level and intervention-level characteristics, results, and study quality. For summarizing adverse events, as most studies used the Radiation Therapy Oncology Group adverse event classification scheme (rtog.org/members/toxicity/ctcmanual.html; rtog.org/members/toxicity/tox.html) in reporting genitourinary and gastrointestinal toxicities after radiation treatments, we have elected to enumerate only grade 3 or greater events in our summary as they are clinically much more serious than grade 1 or grade 2 events. We also used the grade 3 or greater results as proxy for all the toxicity events in the given category. We did not define acute and late adverse events in this review. We accepted definitions that were used in the individual studies (acute events were variably defined as those that occurred less than 3 to less than 6 months after radiation treatments; late events were therefore variably defined as those that occurred more than 3 to more than 6 months after radiation treatments). Result synthesis is presented in the main body of the report. Detailed results of the individual studies are presented in Appendices C to I.

Forest plot

When more than one study provided sufficient data for calculating the effect sizes, we used forest plot to illustrate the relative strength of treatment effects across a set of studies that addressed the same research question (i.e., the same outcome and radiation therapy comparisons). For clinical outcomes, we employed the risk or rate difference (RD) as the metric of choice to quantify the effect size. For each study in the figure, the forest plot shows the effect size (represented by a square) and confidence intervals (represented by horizontal lines). A confidence interval crossing the vertical line of zero effect size indicates a non-statistically significant result. We noted at the bottom of the forest plot the interpretation of the risk or rate difference (e.g., favors LDRBT or favors HDRBT) on left and right side of the plot.

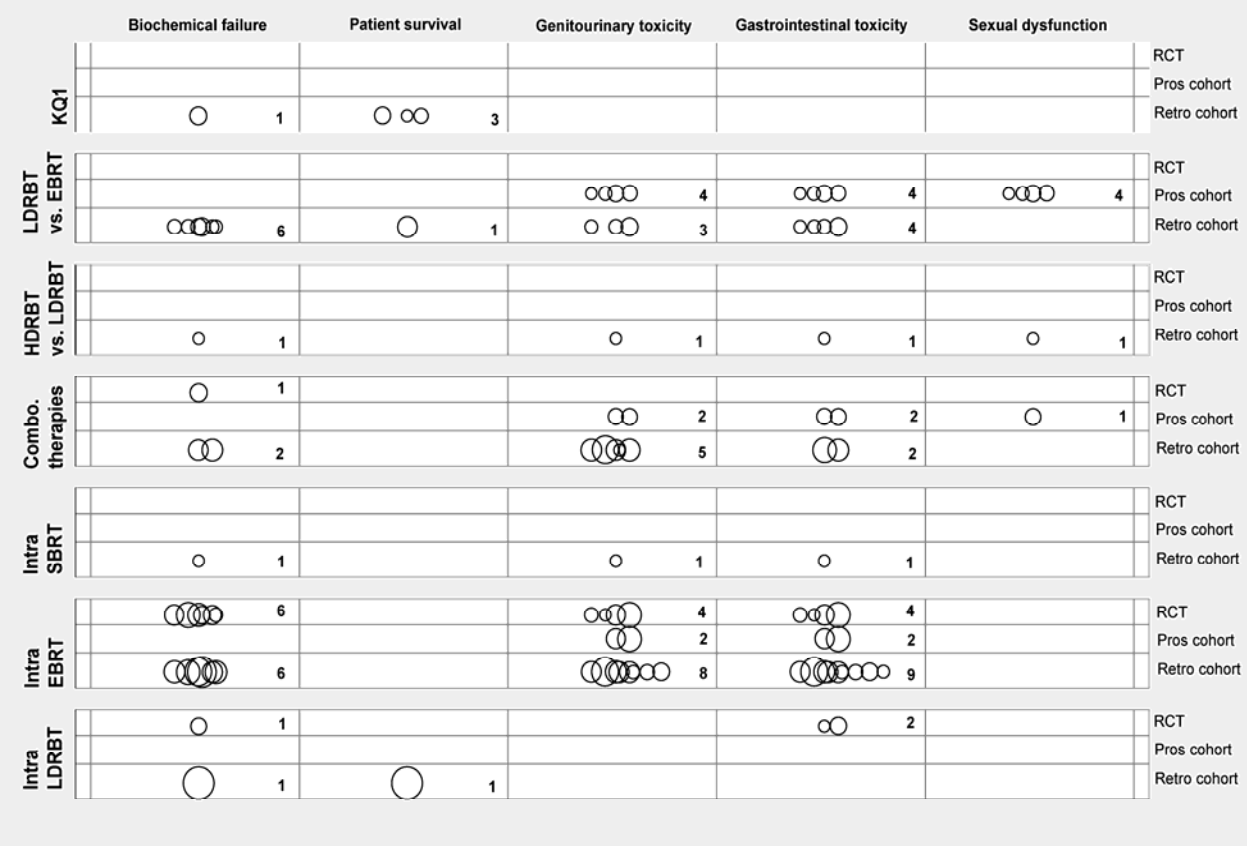
Studies that reported continuous outcomes (i.e., sexual dysfunction score, urinary dysfunction score, bowel dysfunction score, and quality of life score) are not included in the forest plots. Detailed results for these outcomes are summarized in various tables located in the appendices.

Result Synthesis and Strength of Evidence

We searched for articles on radiation treatments for prostate cancer published between January 2007 and December 2009 in MEDLINE® and Cochrane Central database and found 1,283 relevant citations. Abstract screening of these citations identified 165 potentially relevant articles. Full-text screening of these 165 articles identified 53 that met our eligibility criteria. We also added nine RCTs relevant to radiation treatments identified in the Minnesota report to our analysis. A total of 62 articles were included in our review.

The grand overview figure (Figure 2) detailed how many studies reported an outcome (either as a primary or secondary outcome) that is of interest. The total number of studies is greater than the number of unique studies as each study may have provided data for more than one outcome. Table 3 summarized the strength of evidence for the outcomes reported in each of the comparisons. Table 4 summarized only those comparisons with moderate level of evidence.

Figure 2. Number of comparative primary studies on radiation treatments for clinically localized prostate cancer[a]



[a] Because no studies that compared between SBRT and EBRT, SBRT and HDR, SBRT and LDR, or EBRT vs. HDRBT were identified, these comparisons are not listed in this figure.

Table 3. Strength of evidence for radiation treatments of clinically localized prostate cancer

	High	Moderate	Insufficient
KQ1. Radiation therapy versus no treatment or no initial treatment			
Freedom from Biochemical failure			X[a]

Disease Specific Survival		X[b]
GU/GI Toxicity		X[c]
KQ 2. Different forms or doses of radiation		
SBRT versus EBRT		X[a]
SBRT versus HDRBT		X[a]
SBRT versus LDRBT		X[a]
EBRT versus HDRBT		X[a]
EBRT versus LDRBT		
Freedom from Biochemical failure		X[b]
Disease Specific Survival		X[c]
GU/GI Toxicity		X[b]
LDRBT versus HDRBT		
Freedom from Biochemical failure		X[c]
Disease Specific Survival		X[c]
GU/GI Toxicity		X[c]
Combined RT modality comparisons		
Freedom from Biochemical failure		X[c]
GU/GI Toxicity		X[d]
Intra SBRT comparisons		
Freedom from Biochemical failure		X[c]
GU/GI Toxicity		X[c]
Intra EBRT comparisons		
Freedom from Biochemical failure	X[e]	
GU/GI Toxicity	X[e]	
Intra BT comparisons		
Freedom from Biochemical failure		X[f]
GU/GI Toxicity		X[b]
KQ 3. Patient characteristics related to radiation treatment outcomes		
Baseline risk (Stage, PSA, Gleason score)		X[b]
Gleason score/PSA levels		X[c]

a: No study available

b: Results inconsistent across studies

c: Only one study

d: Predominantly C quality studies

e: ≥2 B quality RCTs that reported similar results (significant difference or no difference)

f: Only one RCT and one retrospective study

Table 4. Comparisons with Moderate level of evidence

	Biochemical failure	Genitourinary toxicity	Gastrointestinal toxicity
EBRT dose comparisons	X[a]	X[b]	X[b]
EBRT fraction comparisons	X[c]	X[c]	X[c]

[a] Higher dose EBRT is associated with increased rates of freedom from biochemical failure at 5 to 10 years compared to lower dose EBRT
[b] Little or no difference between higher and lower dose EBRT
[c] Little or no difference between hypofractionation and standard fractionation arms

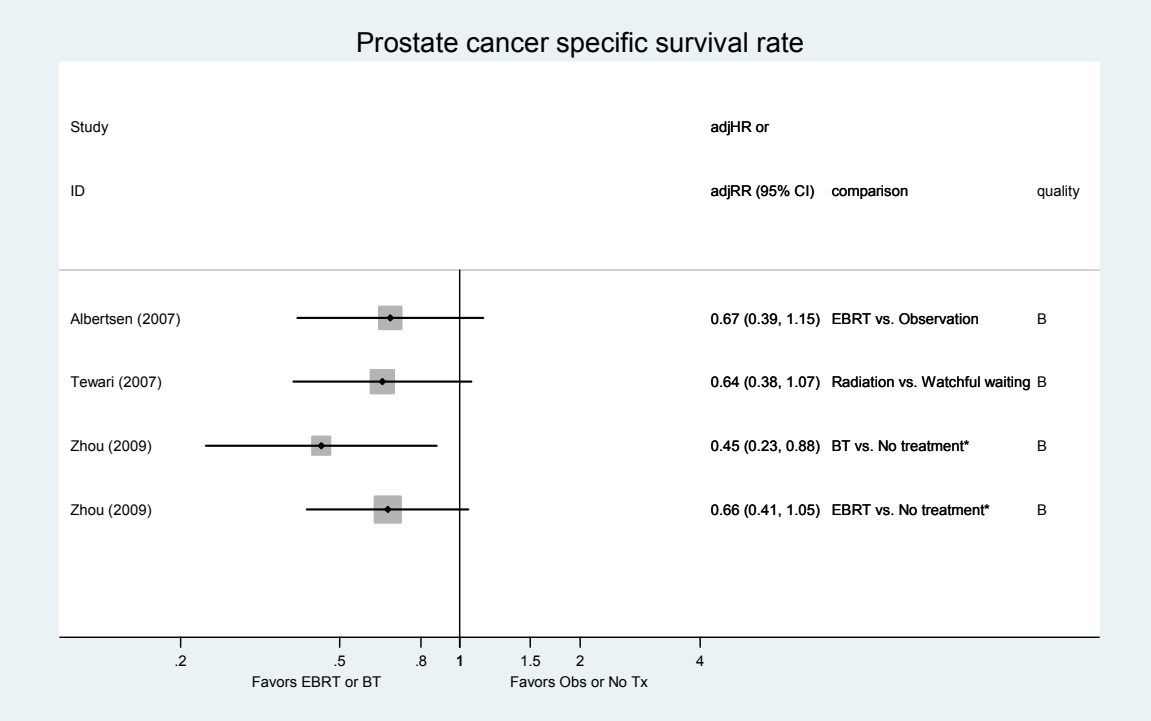
Key question 1: radiation therapy versus no treatment or no initial treatment (Figure 3)

The strength of evidence for comparing radiation therapy with either no treatment or no initial treatment was rated "insufficient" as all five eligible studies were retrospective analyses.[14-18] These B-rated studies mostly provided data on different health outcomes. This makes it difficult to draw adequate conclusions regarding the same health outcome from the aggregate of the few qualified studies. The Minnesota review did not identify any RCTs that compared external beam radiation therapy with watchful waiting; neither did this update review.

Data from three retrospective cohorts showed mostly non-significant improvement in disease-specific survival in those patients who received radiation therapy compared with those who had either no treatment or no initial treatment.[15-17]

Only one study reported genitourinary toxicity outcome[18] and found no difference between BT or EBRT and no treatment or no initial treatment, but higher rate of receiving urethral stricture treatment in patients treated with combined EBRT and BT, compared with those with no treatment or no initial treatment. One study reported incidence of second primary cancer,[14] and found significantly higher rates of second primary cancer in patients treated with EBRT compared with those with no treatment or no initial treatment, but no difference between patients treated with BT and those with no treatment or no initial treatment.

Figure 3. Patient survival: radiation therapy vs. no treatment or no initial treatment



Key question 2: different forms of radiation therapies

SBRT vs. other radiation modalities; EBRT vs. HDRBT

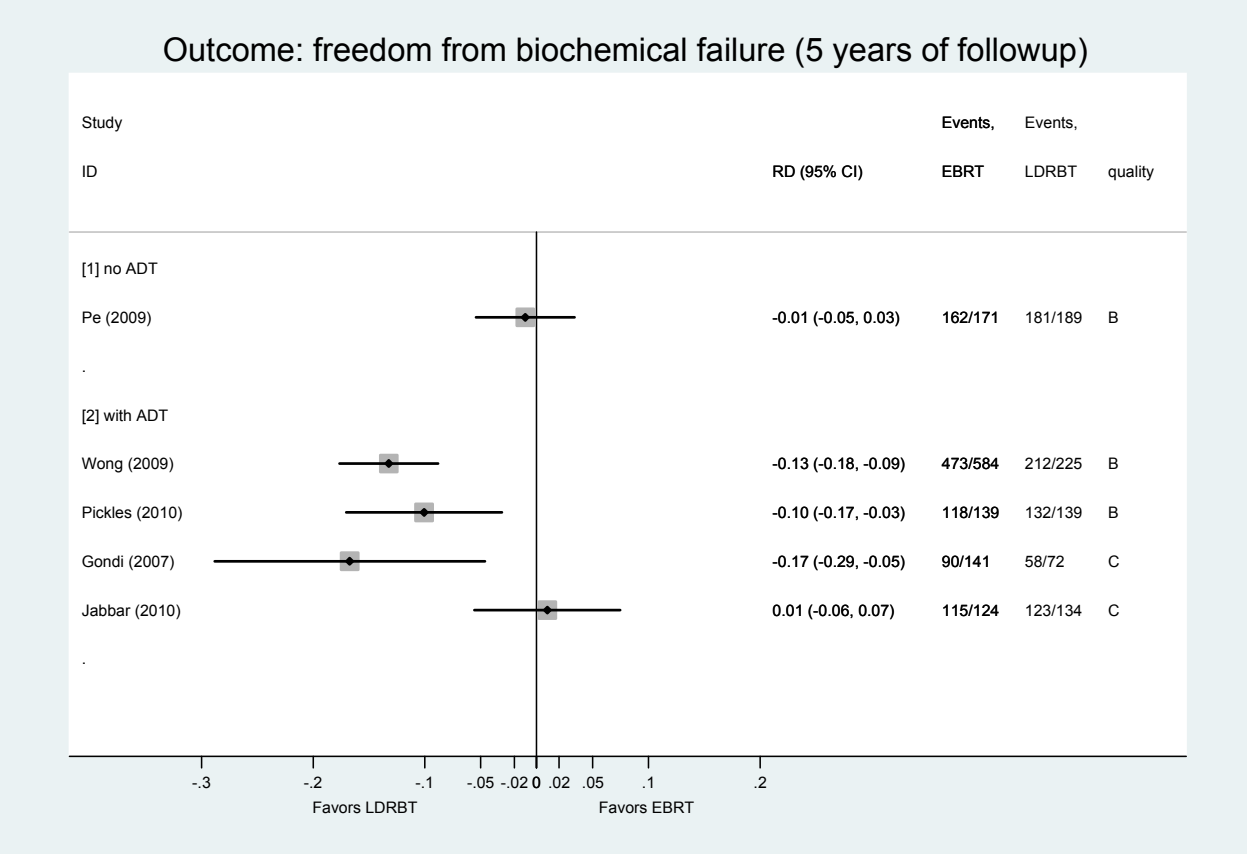
There were no comparisons found between SBRT and any other radiation modality. There were also no comparisons between EBRT and HDRBT.

LDRBT versus EBRT (Tables 5, 6; Figure 4)

The strength of evidence for the comparative efficacy between LDRBT and EBRT on disease specific patient survival was rated "insufficient" as there was only one eligible study in this comparison. This B-rated retrospective comparison did not find a difference in disease specific patient survival comparing LDRBT with EBRT.[17]

The strength of evidence for the comparison between LDRBT and EBRT on biochemical control was rated "insufficient" because the results were inconsistent across the four B-rated retrospective studies.[19-22] While two studies found better biochemical control in the LDRBT group compared with the EBRT group,[21, 22] two studies did not find differences between groups.[19, 20] (N.B. only three B studies were depicted in Figure 4, one B study was not depicted because it did not provide crude rates[20]).

Figure 4. Freedom from biochemical failure (5 years of follow-up): LDRBT vs. EBRT†



*Gondi (2007) comparing BT (with or without ADT) with EBRT (without ADT).
† Eade (2008) was not depicted here because only the actuarial rates and not the crude rates were reported.

Evidence for the comparative efficacy between LDRBT and EBRT for genitourinary and gastrointestinal toxicities was rated "insufficient" because the two prospective[23, 24] and two retrospective[20, 22] B-rated studies did not report consistent results. Two studies showed that LDRBT was associated with significantly more late genitourinary toxicity than EBRT, but no difference in acute toxicity[20, 22] one study showed that LDRBT was associated with more genitourinary toxicity compared with EBRT but the result was non-significant[23] and one study did not find significant difference in genitourinary toxicity between LDRBT and EBRT.[24] For gastrointestinal toxicity, one study showed that LDRBT was associated with less gastrointestinal toxicity compared with EBRT;[24] the other three studies did not find significant difference between LDRBT and EBRT.[20, 22, 23]

Regarding sexual dysfunction, one B-rated prospective cohort study showed significantly better outcomes with LDRBT compared with EBRT,[24] another B-rated prospective cohort study also reported better outcomes with LDRBT compared with EBRT, but the P value of this result was not reported.[23]

Only one study reported cancer incidence.[25] This B-rated retrospective cohort study showed a significantly lower incidence of bladder and rectal cancer with LDRBT compared with EBRT.

Table 5. Genitourinary toxicity: LDRBT vs. EBRT

Outcome	Interventions or comparisons (total sample size)	Study Findings		Quality
Prospective cohort studies				
Disease-specific QoL: urinary scores	LDRBT (N=715) vs. EBRT (N=695)	Sanda (2008)	Worse	B
		Ferrer (2008)	No diff	B
		Litwin (2007) or Gore (2009)	**Worse**[a]	C
		Chen (2009):		C
		- patients with normal function at baseline	No diff	
		- patients with intermediate function at baseline	Better / Worse[b]	
		- patients with poor function at baseline	Worse	
Retrospective cohort studies				
Acute GU ≥ Grade 3	LDRBT (N=383) vs. EBRT (N=800)	Eade (2008)	No diff	B
		Wong (2009)	No diff	B
Late GU ≥ Grade 3	LDRBT (N=383) vs. EBRT (N=800)	Eade (2008)	**Worse**	B
		Wong (2009)	**Worse**	B
Urethral strictures	LDRBT (N=158) vs. EBRT (N=216)	Eade (2008)	**Worse**	B
Incidence of bladder cancer (>10 years of follow-up)	LDRBT (N=22889) vs. EBRT (N=93059)	Nieder (2008)	**Better**	B

Better: net difference in urinary scores improved >1 point or statistically significant risk difference in increasing acute/late GU toxicity or other adverse outcomes, comparing LDRBT with EBRT

No diff: net difference in urinary scores within 1 point or no statistically significant risk difference in acute/late GU toxicity and other adverse outcomes, comparing LDRBT with EBRT

Worse: net difference in urinary scores worsen >1 point or statistically significant risk difference in decreasing acute/late GU toxicity or other adverse outcomes, comparing LDRBT with EBRT

Bold words signify statistical significance P<0.05

[a] Based on the Hazard Ratio of returning to baseline UCLA urinary score comparing the two groups

[b] Better for urinary incontinence score, and worse for urinary obstruction or irritation score

Table 6. Gastrointestinal toxicity: LDRBT vs. EBRT

Outcome	Interventions or comparisons (total sample size)	Study Findings		Quality
Prospective cohort studies				
Disease-specific QoL: bowel scores	LDRBT (N=709) vs. EBRT (N=681)	Sanda (2008)	No diff	B
		Ferrer (2008)	**Better**[a]	B
		Litwin (2007) or Gore (2009)	No diff[b]	C
		Chen (2009)	Better	C
Retrospective cohort studies				
Acute GI ≥ Grade 3	LDRBT (N=275) vs. EBRT (N=767)	Wong (2009)	No diff	B
		Lesperance (2008)	No diff	C
Late GI ≥ Grade 3	LDRBT (N=433) vs. EBRT (N=979)	Eade (2008)	No diff	B
		Wong (2009)	No diff	B
		Lesperance (2008)	No diff	C
Incidence of rectal cancer (>10 years of follow-up)	LDRBT (N=22889) vs. EBRT (N=93059)	Nieder (2008)	**Better**	B

Better: net difference in urinary scores improved >1 point or statistically significant risk difference in increasing acute/late GI toxicity or other adverse outcomes, comparing LDRBT with EBRT
No difference: net difference in urinary scores within 1 point or no statistically significant risk difference in acute/late GI toxicity and other adverse outcomes, comparing LDRBT with EBRT
Worse: net difference in urinary scores worsen >1 point or statistically significant risk difference in decreasing acute/late GI toxicity or other adverse outcomes, comparing LDRBT with EBRT
Bold words signify statistical significance P<0.05
[a] Adjusted for pretreatment score, age at diagnosis, risk group and hormonal treatment using generalized equation models
[b] Based on the Hazard Ratio of returning to baseline UCLA bowel score comparing the two groups

LDRBT vs. HDRBT

The strength of evidence for comparing LDRBT with HDRBT on biochemical outcome was rated "insufficient" as there was only one eligible study in this comparison. This C-rated retrospective cohort study compared HDR using Ir-192 (38 Gy or 42 Gy) with LDRBT using Pd-103 (120 Gy).[26] The study did not find a difference in the 5-year freedom from biochemical failure and sexual dysfunction in the two groups. P values for the difference in genitourinary and gastrointestinal toxicities were not reported.

Combination Therapies (Tables 7, 8)

Evidence on the comparative efficacy of different combinations of radiation was rated "insufficient" as there were only a few studies in each of the comparisons.

There was no difference in biochemical failure between arms in one B-rated RCT comparing LDRBT plus EBRT in different doses.[27]

There was no difference in biochemical or clinical failure in one B-rated RCT comparing EBRT against EBRT plus HDRBT.[28] One B-rated retrospective cohort study (Wong 2009) did not directly compare LDRBT plus EBRT against LDRBT but provided sufficient data for such a comparison; our own analysis showed no significant difference in biochemical control in these two arms.[22]

Our own analysis of the Wong 2009 study found an increase in late genitourinary toxicity in LDRBT plus EBRT compared with EBRT.[22] One B-rated prospective cohort study reported non-significantly higher urinary dysfunction in patients who had EBRT plus LDRBT compared with EBRT plus HDRBT.[29] A B-rated study found a significantly higher rate of urethral strictures in BT plus EBRT compared with EBRT.[18]

Table 7. Genitourinary toxicity: combinations of radiotherapies vs. EBRT or LDRBT

Outcome	Interventions or comparisons (total sample size)	Findings		Quality
Prospective cohort studies				
Disease-specific QoL: urinary scores	HDRBT+EBRT (N=49) vs. LDRBT+EBRT (N=61)	Lev (2009)	Better	B
Acute GU ≥ Grade 3	HDRBT+EBRT (N=40) vs. EBRT (N=57)	Soumarova (2007)	No diff	C
Retrospective cohort studies				
Disease-specific QoL: urinary scores	LDRBT+EBRT (N=15) vs. LDRBT (N=15)	Song (2008)	Worse	C
Acute GU ≥ Grade 3	LDRBT+EBRT (N=44)* vs. EBRT (N=314)	Wong (2009)	No diff	B
	LDRBT+EBRT (N=44)* vs. LDRBT (N=215)	Wong (2009)	No diff	
	LDRBT+EBRT (N=127) vs. LDRBT (N=216)	Zelefsky (2008)	No diff	C
Late GU ≥ Grade 3	LDRBT+EBRT (N=44)* vs. EBRT (N=314)	Wong (2009)	**Worse**	B
	LDRBT+EBRT (N=44)* vs. LDRBT (N=215)	Wong (2009)	No diff	
	LDRBT+EBRT (N=127) vs. LDRBT (N=216)	Zelefsky (2008)	No diff	C
Urethral strictures	BT+EBRT (N=231) vs. EBRT (N=645)	Elliott (2007)	**Worse**	B

QoL, quality of life; diff, difference
Better: net difference in urinary scores improved >1 point or statistically significant risk difference in increasing acute/late GU toxicity or other adverse outcomes, comparing first treatment listed with second treatment listed
No diff: net difference in urinary scores within 1 point or no statistically significant risk difference in acute/late GU toxicity and other adverse outcomes, comparing first treatment listed with second treatment listed
Worse: net difference in urinary scores worsen >1 point or statistically significant risk difference in decreasing acute/late GU toxicity or other adverse outcomes, comparing first treatment listed with second treatment listed
Bold words signify statistical significance P<0.05
*The same LDRBT+EBRT group was compared to EBRT (IMRT) or LDRBT group

Table 8. Gastrointestinal toxicity: combinations of radiotherapies vs. EBRT or LDRBT

Outcome	Interventions or comparisons (total sample size)	Findings		Quality
Prospective cohort studies				
Disease-specific QoL: bowel scores	HDRBT+EBRT (N=49) vs. LDRBT+EBRT (N=61)	Lev (2009)	No diff	B
Acute GI ≥ Grade 3	HDRBT+EBRT (N=40) vs. EBRT (N=57)	Soumarova (2007)	Better	C
Retrospective cohort studies				
Acute GI ≥ Grade 3	LDRBT+EBRT (N=44)* vs. EBRT (N=314)	Wong (2009)	No diff	B
	LDRBT+EBRT (N=44)* vs. LDRBT (N=215)	Wong (2009)	No diff	
	LDRBT+EBRT (N=127) vs. LDRBT (N=216)	Zelefsky (2008)	No diff	C
Late GI ≥ Grade 3	LDRBT+EBRT (N=44)* vs. EBRT (N=314)	Wong (2009)	No diff	B
	LDRBT+EBRT (N=44)* vs. LDRBT (N=215)	Wong (2009)	No diff	
	LDRBT+EBRT (N=127) vs. LDRBT (N=216)	Zelefsky (2008)	No diff	C

QoL, quality of life; diff, difference
Better: net difference in urinary scores improved >1 point or statistically significant risk difference in increasing acute/late GU toxicity or other adverse outcomes, comparing first treatment listed with second treatment listed
No diff: net difference in urinary scores within 1 point or no statistically significant risk difference in acute/late GU toxicity and other adverse outcomes, comparing first treatment listed with second treatment listed
Worse: net difference in urinary scores worsen >1 point or statistically significant risk difference in decreasing acute/late GU toxicity or other adverse outcomes, comparing first treatment listed with second treatment listed

Bold words signify statistical significance P<0.05
*The same LDRBT+EBRT group was compared to EBRT (IMRT) or LDRBT group

Our analysis of the data provided by a B-rated retrospective cohort study showed a higher rate of second primary cancers and late second primary cancers (≥ 5 years) in patients who had EBRT compared with those who had EBRT plus BT.[14]

One B-rated retrospective cohort study did not find significant difference in health-related quality of life between the EBRT group and EBRT plus HDRBT group.[30]

Intra-SBRT comparisons

The strength of evidence for comparative efficacy of stereotactic body radiation therapy was rated "insufficient" as only one study[31] qualified for inclusion in this review (see Appendix H for excluded studies specifically related to CyberKnife®). This C-rated retrospective cohort study with 304 patients and short follow-up found little difference in bladder and rectal toxicities between those who received 35 Gy in 5 fractions and those who received 36.25 Gy also in 5 fractions.

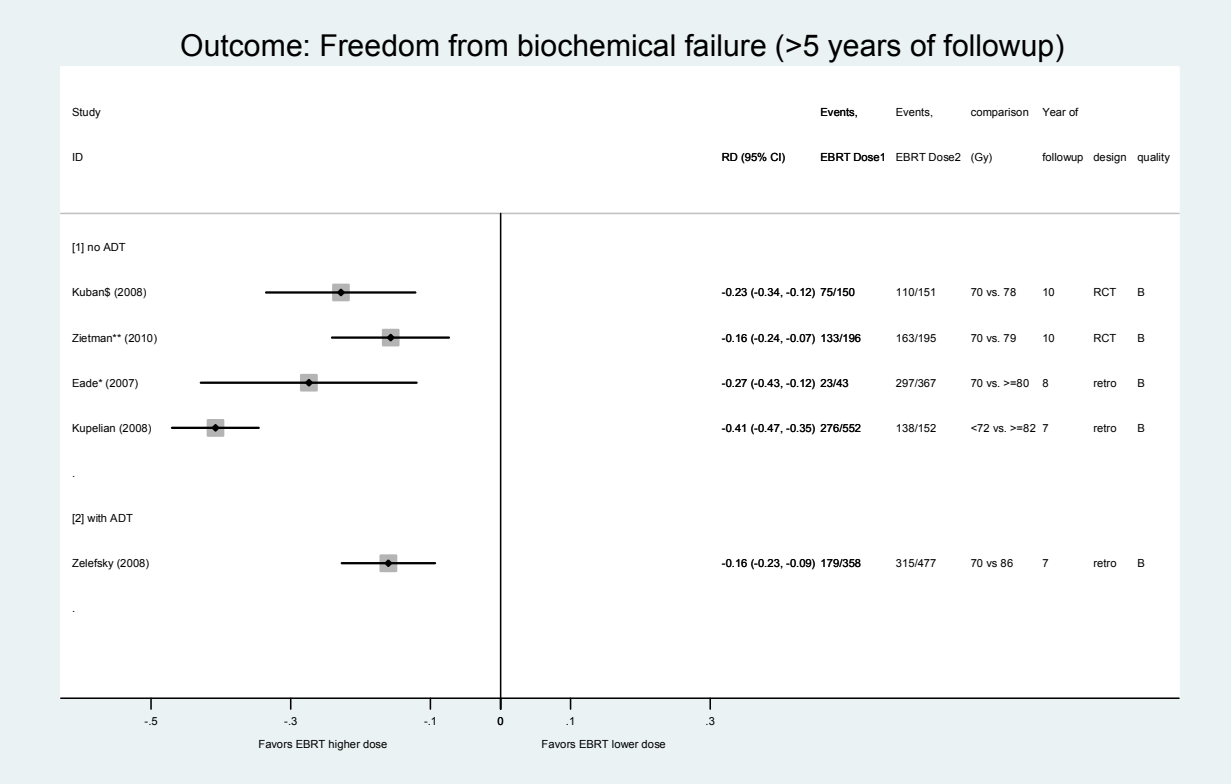
Intra-EBRT Comparisons

Intra-EBRT studies compared different radiation dosages, fractions or modalities. We grouped these studies based on these comparisons.

EBRT Dose Comparisons (Tables 9, 10; Figure 5)

The strength of evidence for EBRT dose comparison studies for freedom from biochemical failure was rated "moderate". Data from three B-rated RCTs in five publications[32-36] and five B-rated retrospective cohort studies[37-40] suggest that the higher dose EBRT is associated with increased rates of freedom from biochemical failure at 5 to 10 years compared to lower dose EBRT.

Figure 5. Freedom from biochemical failure: EBRT dose comparisons (>5 years of follow-up)



$Kuban (2008) also provided 5-year follow-up data; *Eade (2007) also provided 5-year follow-up data; **Zietman 2010 provided follow-up data for patients originally reported in Zietman 2005

The strength of evidence for EBRT dose comparison studies for acute and late genitourinary or gastrointestinal grade 3 or greater toxicities was rated "moderate". Data from five B-rated studies (one RCT,[35] one prospective cohort,[41] three retrospective cohort[22, 38, 42]) suggest that there is little or no difference in acute and late genitourinary or gastrointestinal toxicities between higher and lower dose EBRT.

Table 9. Genitourinary toxicity: EBRT dose comparisons

Outcome	Interventions or comparisons (total sample size)	Study	Findings	Quality
RCTs				
Acute GU ≥ Grade 3	Higher dose (N= 195) vs. lower dose (N= 196)	Zietman (2005)	No diff	B
Late GU ≥ Grade 3	Higher dose (N= 195) vs. lower dose (N= 196)	Zietman (2005)	No diff	B
Prospective cohort studies				
Late GU ≥ Grade 3	Higher dose (N= 958) vs. lower dose (N= 400)	Michalski (2010)	No diff	B
		Lin (2007)	No diff	C
Retrospective cohort studies				
Acute GU ≥ Grade 3	Higher dose (N= 422) vs. lower dose (N= 643)	Wong (2009)	No diff	B
		Jani (2007)	No diff	C
	Higher (N=741[B]) vs. lower dose (N=830 [B])	Zelefsky (2008)[A]	**Higher is worse**	B
Late GU ≥ Grade 3	Higher dose (N= 724) vs. lower dose (N= 799)	Goldner (2009)	No diff	B
		Wong (2009)	No diff	B
		Hanseen (2008)	No diff	C
		Jani (2007)	No diff	C
	High (N=741), medium (N=472), low (N=358)	Zelefsky (2008)[A]	**High is worse**	B

Better: statistically significant risk difference in increasing acute/late GI toxicity or other adverse outcomes, comparing EBRT higher dose with EBRT lower dose
No difference: no statistically significant risk difference in acute/late GI toxicity and other adverse outcomes, comparing EBRT higher dose with EBRT lower dose
Worse: statistically significant risk difference in decreasing acute/late GI toxicity or other adverse outcomes, comparing EBRT higher dose with EBRT lower dose
Bold words signify statistical significance P<0.05
[A] ≥ Grade 2 GU toxicity
[B] estimated; as high (81 Gy) was only worse for those with IMRT, unclear how many without IMRT received high dose

Table 10. Gastrointestinal toxicity: EBRT dose comparisons

Outcome	Interventions or comparisons (total sample size)	Study	Findings	Quality
RCTs				
Acute GI ≥ Grade 3	Higher dose (N= 195) vs. lower dose (N= 196)	Zietman (2005)	No diff	B
Late GI ≥ Grade 3	Higher dose (N= 195) vs. lower dose (N= 196)	Zietman (2005)	No diff	B
Prospective cohort studies				
Late GI ≥ Grade 3	Higher dose (N= 958) vs. lower dose (N= 400)	Michalski (2010)	No diff	B
		Lin (2007)	No diff	C
Retrospective cohort studies				
Acute GI ≥ Grade 3	Higher dose (N= 422) vs. lower dose (N= 643)	Wong (2009)	No diff	B
		Jani (2007)	No diff	C
	High (N=741), medium (N=472), low (N=358)	Zelefsky (2008)[A]	No diff[A]	
Late GI ≥ Grade 3	Higher dose (N= 724) vs. lower dose (N= 799)	Goldner (2009)	No diff	B
		Wong (2009)	No diff	B
		Hanseen (2008)	No diff	C
		Jani (2007)	No diff	C
	High (N=741), medium (N=472), low (N=358)	Zelefsky (2008)[A]	**medium is worst**	B

Better: statistically significant risk difference in increasing acute/late GI toxicity or other adverse outcomes, comparing EBRT higher dose with EBRT lower dose
No difference: no statistically significant risk difference in acute/late GI toxicity and other adverse outcomes, comparing EBRT higher dose with EBRT lower dose
Worse: statistically significant risk difference in decreasing acute/late GI toxicity or other adverse outcomes, comparing EBRT higher dose with EBRT lower dose
Bold words signify statistical significance $P<0.05$
[A] ≥ Grade 2 GI toxicity

Standard vs. Hypofractionation EBRT Comparisons (Tables 11, 12)

The strength of evidence for EBRT fractionation comparison studies for freedom from biochemical failure was rated "moderate". Data from three B-rated studies (two RCTs,[43, 44] and one retrospective cohort[45]) suggest that there is no difference between hypofractionation and standard fractionation arms as performed for freedom from biochemical failure.

The strength of evidence for EBRT fractionation comparison studies for acute and late genitourinary/gastrointestinal grade ≥3 toxicities was rated "moderate". Data from three B-rated studies (two RCTs,[43, 46] one retrospective cohort[45]) suggest that there is little or no difference between hypofractionation and standard fractionation arms for acute and late gastrointestinal toxicities. One B-rated RCT showed that the acute genitourinary toxicity was significantly slightly higher in the hypofractionation arm compared with the standard fractionation arm but there was no difference in the late genitourinary toxicity.[43] No differences were found in the acute or late genitourinary toxicity in the other studies.

Table 11. Genitourinary toxicity: EBRT fraction size comparisons

Outcome	Interventions or comparisons (total sample size)	Study	Findings	Quality
RCTs				
Acute GU ≥ Grade 3	EBRT (Long arm: 66 Gy in 33 fractions) (N=470) vs. EBRT (Short arm: 52.5 Gy in 20 fractions) (N=466)	Lukka (2005)	**Long arm is better**	B
	Conventional fractionation (N=50) vs. hypofractionation IMRT (N=50)	Pollack (2006)	No diff	B
Late GU ≥ Grade 3	EBRT (Long arm: 66 Gy in 33 fractions) (N=470) vs. EBRT (Short arm: 52.5 Gy in 20 fractions) (N=466)	Lukka (2005)	No diff	B
Retrospective cohort studies				
Acute GU ≥ Grade 3	Standard fractionation (N=74) vs. hypofractionation-3Gy/fraction (N=22) vs. hypofractionation-3.15Gy/fraction EBRT (N=34)	Leborgne (2008)	No diff	C
Late GU ≥ Grade 3	Standard fractionation (N=130) vs. hypofractionation EBRT (N=89)	Leborgne (2009)	No diff	B

Better: statistically significant risk difference in increasing acute/late GI toxicity, comparing EBRT fraction sizes
No difference: no statistically significant risk difference in acute/late GI toxicity, comparing EBRT fraction sizes
Worse: statistically significant risk difference in decreasing acute/late GI toxicity, comparing EBRT fraction sizes
Bold words signify statistical significance P<0.05

Table 12. Gastrointestinal toxicity: EBRT fraction size comparisons

Outcome	Interventions or comparisons (total sample size)	Study	Findings	Quality
RCTs				
Acute GI ≥ Grade 3	EBRT (Long arm: 66 Gy in 33 fractions) (N=470) vs. EBRT (Short arm: 52.5 Gy in 20 fractions) (N=466)	Lukka (2005)	No diff	B
	Conventional fractionation (N=50) vs. hypofractionation IMRT (N=50)	Pollack (2006)	No diff	B
Late GI ≥ Grade 3	EBRT (Long arm: 66 Gy in 33 fractions) (N=470) vs. EBRT (Short arm: 52.5 Gy in 20 fractions) (N=466)	Lukka (2005)	No diff	B
Retrospective cohort studies				
Acute GI ≥ Grade 3	Standard fractionation (N=74) vs. hypofractionation-3Gy/fraction (N=22) vs. hypofractionation-3.15Gy/fraction EBRT (N=34)	Leborgne (2008)	No diff	C
Late GI ≥ Grade 3	Standard fractionation (N=130) vs. hypofractionation EBRT (N=89)	Leborgne (2009)	No diff	B

Better: statistically significant risk difference in increasing acute/late GI toxicity, comparing EBRT fraction sizes
No difference: no statistically significant risk difference in acute/late GI toxicity, comparing EBRT fraction sizes
Worse: statistically significant risk difference in decreasing acute/late GI toxicity, comparing EBRT fraction sizes
Bold words signify statistical significance P<0.05

Different variations of EBRT Comparisons

The strength of evidence for the following variations of EBRT administration was all rated insufficient as there was only one study for each variety of comparison.

One B-rated RCT compared EBRT with or without using endorectal balloon for prostate immobilization. [47] There were no differences in the acute and chronic genitourinary or gastrointestinal toxicity ≥ grade 3 in the two groups (no events in either group). In terms of chronic gastrointestinal toxicity ≥ grade 3 comparing EBRT with endorectal balloon versus without endorectal balloon, it was 0% versus 4% (no P value reported).

One C-rated prospective cohort study compared patients who received conformal radiotherapy to the prostate only (CRT-PO) with patients who received whole pelvis and prostate boost radiotherapy (WP+PB). [48] The study reported patients who had WP+PB had increased radiation induced fatigue compared with patients who had CRT-PO.

One B-rated retrospective cohort study evaluated the effect of different 3D-CRT nodal target coverage on biochemical failure-free survival (bFFS).[49] Some patients had mini pelvis (MP) field treatment (excluding common iliac nodes) and some had whole pelvis (WP) field treatment (including common iliac nodes). This study observed that the pretreatment PSA level, Gleason score, T stage, and the use of ADTs were predictors of treatment response. An increase in bFFS in the MP field arm compared to the WP field arm was observed on univariate analysis, but not on multivariate analysis.

One C-rated retrospective study compared the effects of 3D-CRT versus 2D-CRT on anorectal function. There was no difference in the chronic grade ≥3 rectal toxicity at 2 years.[50]

Intra-LDRBT comparisons

The strength of evidence for LDRBT dose comparison or radionuclide comparison studies for freedom from biochemical failure was rated "insufficient" because there were few studies within each comparison.

One B-rated RCT with three interim analyses found little or no difference between I-125 (144 Gy) and Pd-103 (125 Gy) in terms of freedom from biochemical failure at 3 to 6 years or genitourinary or gastrointestinal toxicities.[51-53]

One B-rated retrospective cohort study showed that higher biological effective dose (BED) (>220 Gy) using either I-125 or Pd-103 improved the overall survival rate and 5-year rate of freedom from biochemical failure compared with lower dose (≤220 Gy) in those with higher risk of prostate cancer progression (Gleason score 8 to 10).[54, 55]

One C-rated RCT comparing use and non-use of rectal protection with injection of hyaluronic acid among patients of LDRBT (I-125, 145 Gy) showed no difference in rectal bleeding.[56]

Key question 3: patient characteristics as a modifier of outcomes of radiation therapies (Table 13)

The strength of evidence for evaluating baseline risk as a modifier of outcomes of radiation therapies was rated "insufficient" . Five B-rated studies reported that treatment outcomes differed across low, intermediate, and high risk patient groups, but there were limited studies available for the comparisons reviewed.[15, 22, 32, 40, 54]

The strength of evidence for evaluating Gleason score and baseline PSA concentration as modifiers was also rated "insufficient" because there were only two eligible studies (one for each characteristic, both B-rated) that conducted the analyses.[32, 33, 55] There was no difference in treatment outcomes between patients with different Gleason score or baseline PSA concentration.

Table 13. Effects of patient characteristics on treatment outcomes of different radiation therapies

Author Year [UI]	Treatment comparison	Analysis by factor of interest	Quality
Baseline risk on biochemical failure			
Albertsen 2007 [17296379]	EBRT vs. observation	Low risk – ▲survival rate in EBRT (P value not reported) Intermediate risk – ▲survival rate in EBRT (P value not reported) High risk - ▲survival rate in EBRT (P value not reported)	B
Kuban 2008 [17765406]	3D-CRT 78 Gy vs. 70 Gy	Low risk – ▲FFF in 78 Gy (P = 0.042) Intermediate risk – no difference High risk – ▲FFF in 78 Gy (P = 0.004)	B
Stone 2007 [17689026]	BT < 140 Gy, 140-200 Gy, > 200 Gy	Low risk - ▲FFF in higher dose (P < 0.0001) Intermediate risk - ▲FFF in higher dose (P < 0.0001) High risk - ▲FFF in higher dose (P < 0.0001)	B
Wong 2009 [19670452]	conventional dose 3D-CRT, high-dose IMRT, BT alone, or EBRT + BT	Low risk – no difference Intermediate risk – FFF: conventional dose 3D-CRT< BT alone < high-dose IMRT < EBRT + BT (P = 0.0003) High risk – no difference	B
Zelefsky 2008 [18280056] (452)	3D-CRT or IMRT 70.2, 75.6, 81, 86.4 Gy	Low risk– no difference Intermediate risk– ▲ PSA-relapse free survival in the 75.6 Gy or 81 Gy group compared with 70.2 Gy or 86.4 Gy groups (P < 0.0001); ▲rate of distant metastases free survival in 81 Gy compared with 75.6 Gy (P = 0.04) High risk– ▲ PSA-relapse free survival with ▲dose (P < 0.0001); ▲rate of distant metastases free survival in 81 Gy compared with 70.2 Gy (P = 0.01)	B
Baseline PSA concentration			
Kuban 2008 [17765406] Pollack 2002 [2128107]	3D-CRT 78 Gy vs. 70 Gy	PSA >10 ng/ml – ▲FFF in 78 Gy (P < 0.001); no difference in rate of distant metastases free survival PSA ≤ 10 ng/ml – no difference	B
Gleason Score			
Stone 2009 [18597953]	BT < 200 Gy, 200-220 Gy, >220 Gy	score 7 – no difference score 8-10 - ▲FFF with ▲dose (P < 0.001)	B
Interaction between baseline risk category and baseline PSA concentration			
Kuban 2008 [17765406] Pollack 2002 [2128107]	3D-CRT 78 Gy vs. 70 Gy	The difference in treatment between patients with PSA >10 ng/ml and patients with PSA <10 ng/ml was present among intermediate- and high-risk patients, but not among low-risk patients.	B

FFF: freedom from failure rate

Discussion

Because prostate cancer tends to have a long clinical course typically measured in decades, many studies focused on short term adverse events or biochemical control rather than long term clinical efficacy outcomes like metastases and disease-specific mortality. It should be noted that in the studies reviewed, the event rates for grade 3 or greater urinary or bowel toxicity is so low that any statistically significant differences between treatment arms may not translate into substantive clinical differences. It should also be underscored that none of the studies provided adverse events data related to the administration of radiation treatments themselves (e.g., errors in treatment planning software and radiation equipment operation leading to adverse outcomes).

Many of the findings reported in this review were inconsistent for each of the outcomes of interest. The studies reviewed showed substantial heterogeneity. Even among patients with T1 or T2 prostate cancer, the underlying risk of prostate cancer progression varies widely, as this risk is also dependent on Gleason score, pretreatment PSA concentration, and other factors. An important weakness in many of these comparative analyses is that patients were given treatments tailored to their individual risk profile (e.g., patients with low risk prostate cancer tend to be given BT versus those with intermediate risk prostate cancer tend to be given EBRT); this makes it difficult, if not impossible, to assess the comparative efficacies between two forms of radiation treatments as the underlying risk of prostate cancer progression in the two groups of patients may be fundamentally different. Another problem is the fact that many of the techniques of radiation delivery reported in the observation cohorts had evolved over the study period of interest. As a result, one could never be certain that one form of radiation delivered to one patient at one time point is comparable to the "same" form of radiation delivered to another patient at another time point. Some of the other limitations in these analyses include the use of historical controls and lack of adjustment for potential confounders.

As had been noted in the Minnesota report, patients from minority groups were underrepresented in the studies reviewed. Although no study examined whether outcomes of different radiation treatments differ among racial groups, Rose et al. reported that the probability of receiving any aggressive therapy or BT did not differ between patients of non-Hispanic black and non-Hispanic white races.[57] However, non-Hispanic white patients were more likely to receive radical prostatectomy and less likely to receive radiation therapy when compared with non-Hispanic blacks.

Many of the studies did not report a power calculation. Even though some of the studies included cohorts with relatively large numbers of subjects (thousands), it is plausible that, in fact, the included studies may have been underpowered to detect the true effect sizes. Also, the blinding of patients to the intervention as well as that of investigators who measured the outcomes of interest was rarely reported.

The focus of this review is clinically localized prostate cancer (stages T1 and T2). The majority of the patients in these studies had clinically localized disease (stage T1 and T2); however, approximately one-third of the studies reviewed included up to 20% of patients with stage T3 or higher disease. Excluding them would lead to a drastically reduced number of qualified studies and may inadvertently discard useful data. Similarly, approximately half of the studies had some patients who received androgen deprivation therapies (ADTs), either as a neoadjuvant, concurrent or adjuvant therapy. Many of the studies that included patients with stage T3 or higher disease or ADTs did not report results stratified by patients' tumor stage or ADT use. Therefore, we are not always able to draw conclusions on the specific treatment

effects of the different forms of radiation alone for clinically localized prostate cancer patients (stage T1 and T2), without contamination of results from patients with stage T3 or higher disease, or without contamination of results from patients also treated with ADTs. How these contaminations would affect the "true" treatment effect estimate of radiation alone in only T1-T2 disease is unpredictable.

Further complicating our analysis are the heterogeneous definitions used in the various outcomes of interest. For example, for urinary and bowel toxicity, even though the majority of the studies used the Radiation Therapy Oncology Group (RTOG) classification scheme, a minority of the studies reported the actual events (e.g., urinary urgency, rectal bleeding) without using the RTOG scheme. Some studies classified biochemical failure strictly using PSA concentration characteristics; some studies classified clinical failure (without PSA characterization) as a subgroup of biochemical failure. All these differences make cross-study comparison challenging.

Similar to the Minnesota review, we did not identify any completed RCTs that compared the benefits and harms between no treatment or no initial treatment and radiation therapy. Currently, two trials are being carried out to evaluate this question (see further details in Future Research). The number of trials is small. This is likely due to the long survival of those patients with localized disease which poses logistic and financial constraints in conducting trials with long duration of follow-up and the pragmatic difficulty of informing prospective enrollees about the clinical equipoise of watchful waiting and radiation therapy as opinions on these two different options abound on the web and among the different specialists taking care of patients with prostate cancer.

Of note, as an *a priori* decision for this technology assessment, we only looked at the direct evidence comparing radiation treatment with no treatment (or no initial treatment) or one form of radiation treatment versus another form of radiation treatment. We did not examine the indirect evidence from cohort studies or other forms of comparisons. We are aware that one randomized trial comparing radiation therapy with concurrent androgen deprivation therapy to androgen deprivation therapy alone in patients with predominately T3 stage prostate cancer reported a survival benefit for the concurrent radiation therapy arm.[58] While this trial argues indirectly for a beneficial effect of radiation therapy in the treatment of such patients, direct comparative study should be undertaken in appropriately selected clinically localized prostate cancer patients to either confirm or refute this conjecture.

Conclusion

Definitive benefits of radiation treatments compared to no treatment or no initial treatment for localized prostate cancer could not be determined because available data were insufficient. Data on comparative effectiveness between different forms of radiation treatments (BT, EBRT, SBRT) are also inconclusive whether one form of radiation therapy is superior to another form in terms of overall or disease-specific survival. Studies suggest that higher EBRT dose results in increased rates of long-term biochemical control than lower EBRT dose. EBRT administered as a standard fractionation or moderate hypofractionation does not appear to differ with respect to biochemical control and late genitourinary and gastrointestinal toxicities. Available data suggest that BT might be associated with an increase in genitourinary toxicity compared with EBRT. BT appears to be largely comparable to EBRT in the rates of gastrointestinal toxicity. However, more and better quality studies are needed to either confirm or refute these suggested findings.

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Future Research

Whether there is a benefit of radiation treatments compared to no treatment or no initial treatment for men with localized prostate cancer in the PSA era, and for which men, is not clear. To definitively evaluate the effects of radiation treatments compared to no treatment or no initial treatment, well-conducted RCTs with very long follow-up are needed. There are now two ongoing randomized trials enrolling over 2,000 patients each, comparing active surveillance to radical prostatectomy and radiation therapy. The Canadian-sponsored START trial is planning to enroll 2,130 men, with estimated primary completion date of April 2023 (NCT00499174). The British ProtecT trial is planning to enroll 2,050 men, with estimated primary completion date of December 2013 (NCT00632983). Results from these trials should help to answer the questions of which men can be safely observed and which men need therapy, and how radiation therapy and radical prostatectomy compare to each other as the primary treatment approach.

As our review has shown, the available evidence does not permit one to assess the optimal dose and fractionation schedule for external beam radiation therapy. There are at least 4 ongoing trials examining different hypofractionated schedules (NCT00331773, NCT00392535, NCT00667888, NCT00304759). But no trials evaluating hypofractionation used or are using fewer than 15 fractions, including schedules using one to few fractions currently being delivered with high-dose rate brachytherapy and stereotactic body radiation therapy. Randomized trials to address the question of such approaches using one to few fractions (SBRT or HDRBT) should be conducted.

Randomized comparisons of brachytherapy and external beam radiation therapy will also be useful in clarifying the potential relative benefits and harms of the two forms of radiation therapy. The data gathered will help improve counseling of patients as some patients treated now with brachytherapy may also be good candidates for active surveillance.

Our current review did not identify any comparative studies evaluating the role of particle radiation therapy (e.g., proton) in the treatment of prostate cancer. Data from such studies will help decide how to best use these limited resources.

To definitively assess which form and dose of radiation delivered is optimal in minimizing toxicities and prolonging survival and at the same time taking into account patients' own preferences is not a simple task. It would be ideal if one always has the resources to conduct a well-designed RCT to make this assessment. As this is not always possible, a prospectively designed cohort study taking into account important confounders along with a cost-effective method for appropriate long-term follow-up may be more pragmatic under certain circumstances. Retrospective analysis, with its attendant limitations (detailed in Discussion), will continue to be conducted. One is reminded that findings from retrospective analyses are sometimes useful in generating hypotheses for new experimental trials and may also provide valuable data on anticipated and unanticipated adverse events related to the various treatments.

Lastly, as has been mentioned earlier, no studies that we reviewed for this technology assessment reported safety data related to the delivery of radiation (e.g., errors in planning software, operator errors, machine malfunctions), it is vital that safety in radiation delivery be actively monitored and diligently recorded for every patient undergoing any form of radiation treatment.

Appendix A. Search Strategy

Prostate cancer and Radiotherapy
EBM (RCT, HTA, SR), and MEDLINE (1950-2009, in process) 5th Jan 2010

#	Search strategy
1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized controlled trials/
4	Random Allocation/
5	Double-blind Method/
6	Single-Blind Method/
7	clinical trial.pt.
8	Clinical Trials.mp. or exp Clinical Trials/
9	(clinic$ adj25 trial$).tw.
10	((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
11	Placebos/
12	placebo$.tw.
13	random$.tw.
14	trial$.tw.
15	(randomized control trial or clinical control trial).sd.
16	(latin adj square).tw.
17	Comparative Study.tw. or Comparative Study.pt.
18	exp Evaluation studies/
19	Follow-Up Studies/
20	Prospective Studies/
21	(control$ or prospectiv$ or volunteer$).tw.
22	Cross-Over Studies/
23	or/1-22
24	exp prostatic neoplasms/
25	exp radiotherapy/
26	*"Prostatic Neoplasms"/rt [Radiotherapy]
27	(act$ adj3 surve$).mp.
28	(watch$ adj3 wait$).mp.
29	Intensity modulated$.mp. [mp=ti, ot, ab, nm, hw, ui, tx, kw, ct, sh]
30	charged particle beam$.mp. [mp=ti, ot, ab, nm, hw, ui, tx, kw, ct, sh]
31	brachytherapy/
32	radiation therap$.mp. [mp=ti, ot, ab, nm, hw, ui, tx, kw, ct, sh]
33	stereotactic radiosurger$.mp. [mp=ti, ot, ab, nm, hw, ui, tx, kw, ct, sh]

34	conformal radiotherap$.mp. [mp=ti, ot, ab, nm, hw, ui, tx, kw, ct, sh]
35	exp radiosurgery/
36	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37	24 and 36
38	23 and 37
39	limit 38 to english language [Limit not valid in CDSR,CCTR; records were retained]
40	limit 39 to yr="2007 -Current"
41	remove duplicates from 40
42	prostate cancer.mp. or exp prostatic neoplasms/ [mp=ti, ot, ab, nm, hw, ui, tx, kw, ct, sh]
43	23 and 42
44	36 and 43
45	limit 44 to english language [Limit not valid in CDSR,CCTR; records were retained]
46	limit 45 to yr="2007 -Current"
47	46 not 41

Cyberknife search: Ovid MEDLINE(R) 1950 to January Week 4 2010

#	**Search strategy**
1	cyberknife.mp.
2	prostatic neoplasms.mp. or exp Prostatic Neoplasms/
3	1 and 2

Appendix B. Detailed results for the comparison between radiation therapy and no treatment or no initial treatment

Key Question 1. What are the benefits and harms of radiation therapy for clinically localized prostate cancer compared to no treatment or no initial treatment (watchful waiting, active surveillance, or observation) in terms of clinical outcomes?

Randomized controlled trials (RCTs) and Prospective studies

We did not identify eligible RCTs or prospective cohort studies that compared the benefits and harms in radiation therapy versus no treatment or no initial treatment.

Retrospective studies (Table B1)

Five retrospective cohorts reported comparisons between radiation therapy and watchful waiting.[14-18] One study included only patients with T1 or T2 disease,[15] while the other four studies included some patients with T3 or higher stage disease. One study did not specify patients' T stage, but included only patients with localized disease.[16]

Patient survival (Figure B1)

Of the four analyses reported in three registry studies that compared survival between observation and radiation therapy,[15-17] one found lower disease-specific mortality rates in radiation therapy patients compared with patients with no treatment or no initial treatment. In the Ohio CALD study that included patients with local/regional cancer on BT (N = 595), EBRT (N = 783), or no treatment or no initial treatment (N = 1716), compared with patients without treatment (or without initial treatment), disease-specific mortality rates were significantly lower among patients who received BT [adjHR: 0.45 (95%CI, 0.23 to 0.87)], and non-significantly lower among those who received EBRT [adjHR: 0.66 (95%CI, 0.41 to 1.04)], after adjusting for age, race, tumor stage, Gleason score, pretreatment comorbidity, and treatment modalities. [17] The Connecticut Tumor Registry study that analyzed 816 patients with T1 or T2 prostate cancer reported that patients in the observation arm had a non-significant greater prostate cancer mortality rate compared with patients who received EBRT [adjHR: 1.5 (95%CI, 0.9 to 2.6)], after adjusting for age at diagnosis, pretreatment Gleason score, PSA, clinical stage, and Charlson comorbidity score. [15] Similarly, in the Henry Ford Health System tumor registry, disease-specific mortality rates were non-significantly lower among patients on radiation therapy (N = 137) compared with patients on watchful waiting (N = 197) [adjHR: 0.64 (95%CI, 0.38 to 1.06); P = 0.081], after adjusting for race, age at diagnosis, socioeconomic status, Charlson score, year of diagnosis**.** [16] The methodological quality of all three retrospective studies were rated B.

Genitourinary toxicity

A study based on the CaPSURE^{TM} database with 2.7 year follow-up of prostate cancer patients who had watchful waiting (N = 378), EBRT (N = 645), BT (N = 799) or combined EBRT and BT (N = 231) reported that patients on the combined therapy had a significantly higher rate of receiving urethral stricture treatment compared with patients on watchful waiting, after adjusting for age at primary treatment and BMI [adjHR: 4.56 (95%CI, 1.23 to 16.88)]. [18] There was no difference between watchful waiting and EBRT or watchful waiting and BT. The

methodological quality of this study was rated B. The number of patients lost to follow-up was unclear.

Other adverse outcome - second primary cancer

A report based on the Surveillance, Epidemiology, and End Results (SEER) database compared patients who had watchful waiting (N = 40,733), EBRT (N = 48,400), BT (N = 10,233) or combined EBRT and BT (N = 9,096).[14] Compared to patients in the watchful waiting arm, those who received EBRT had a significantly higher rate of second primary cancer (adjHR: 1.14; 95%CI, 1.09 to 1.19) and late second primary cancer (after ≥ 5 years) (adjHR: 1.26; 95%CI, 1.17 to 1.37), after adjusting for age at prostate cancer diagnosis, race/ethnicity, and grade of primary prostate cancer. There was no difference between watchful waiting and BT or combined therapy. The methodological quality of this study was rated B.

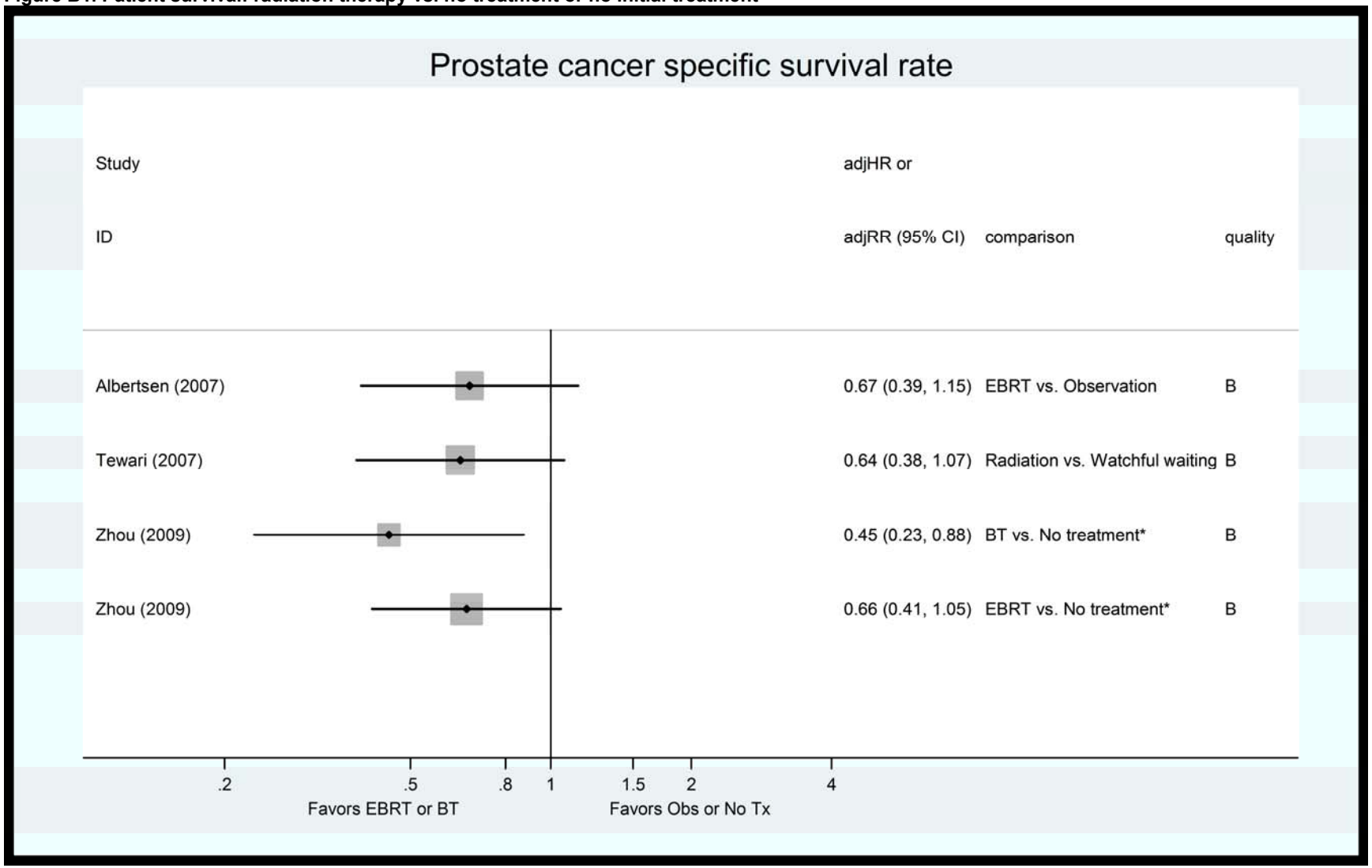
Table B1. Characteristics of retrospective cohort studies that compared radiation therapy with no treatment or no initial treatment

Author Year [UI] Country	Intervention or comparison	N	Mean age, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobili-zation technique	Applied margins for PTV	Planning algorithm	Quality comments
Abdel-Wahab M 2008 [18374503] US	Radiation therapy (BT, EBRT, or BT + EBRT)	67719	69.4	Hispanic White 4.9 Non Hispanic White 76.8 Non-Hispanic Black 11.7 Other non-Hispanic 6.5	82.1	nd	nd	nd	nd	nd	nd	nd	nd	B
	Watchful waiting	40733	73.1	Hispanic White 7.0 Non Hispanic White 72.9 Non-Hispanic Black 13.3 Other non-Hispanic 6.8	78.1	nd	nd	nd	nd	nd	nd	nd	nd	
Albertsen 2007 [17296379] US	EBRT	702	71	nd	100	0-3.9: 27 4-9.9: 44 10-10: 17 20-49: 12	2-4: 17 5: 15 6: 46 7: 11 8-10: 11	nd	nd	nd	nd	nd	nd	B
	Observation	114	70	nd	100	0-3.9: 9 4-9.9: 39 10-10: 29 20-49: 23	2-4: 3 5: 6 6: 46 7: 25 8-10: 20	nd	nd	nd	nd	nd	nd	

Author Year [UI] Country	Intervention or comparison	N	Mean age, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobili-zation technique	Applied margins for PTV	Planning algorithm	Quality comments
Elliott 2007 [17570425] US	Watchful waiting, BT, EBRT, BT + EBRT	6597[C]	>60yr 25 60-69 40 ≥ 70 35	White 87 Black 9 Other 4	98	≤4: 14 4.1-10: 62 10.1-20: 16 >20: 8	2-6: 65 7: 26 8-10: 9	nd	nd	nd	nd	nd	nd	B com-2
Tewari 2007 [17296374] US	Radiation	137	53.5	White 54.0 Black 46.0	nd	nd	nd	26	nd	nd	nd	nd	nd	B
	Watchful waiting	197	52.1	White 46.2 Black 53.8	nd	nd	nd	80	nd	nd	nd	nd	nd	
Zhou 2009 [18538495] US	EBRT, BT, no treatment or no initial treatment[A]	10179 [D]	60-69 21.5 70-74 32.1 ≥ 75 46.5	White or other 91 Black 9	nd	nd[B]	<7: 66.4 7-10: 23.8 Unknown: 9.8	nd	nd	nd	nd	nd	nd	B

nd, no data or not done
[A] No treatment or no initial treatment was defined as no definitive therapy within 6 months of the prostate cancer diagnosis
[B] Tumor was categorized as local-regional in 81.1% of patients, distant metastases 4.6% of patients, and unknown in 14.3% of patients
[C] Including 3310 surgery patients, 199 cryosurgery patients, 73 surgery and EBRT patients, and 961 ADT patients
[D] Including 936 surgery patients, 2947 ADT only patients, and 4776 combination therapy patients
com-1: No adjustment for potential confounders
com-2: incomplete reporting (e.g., little or no description of study eligibility criteria or methods, missing data)
com-3: historical comparison
com-4: incomplete statistical analysis (e.g., P value not reported)
com-5: different lengths of follow-up between groups
com-6: baseline participant characteristics not entirely comparable between groups (no adjustment)
com-7: loss to follow-up ≥20% (only for RCTs)
com-8: method of randomization not reported

Figure B1. Patient survival: radiation therapy vs. no treatment or no initial treatment



* No treatment or no initial treatment was defined as no definitive therapy within 6 months of the prostate cancer diagnosis

Appendix C. Detailed results for the comparison between LDRBT vs. EBRT; HDRBT vs. LDRBT

LDRBT vs. EBRT (Tables C1-C8; Figures C1-C2)

Randomized controlled trials (RCTs)

There were no randomized controlled trials comparing LDRBT versus EBRT for the treatment of localized prostate cancer that met our inclusion criteria.

Prospective studies (Table C1)

Four prospective cohort studies in five publications reported comparisons between LDRBT and EBRT. [23, 24, 59-61] The sample size in these studies ranged from 168 to 598. Two studies included only patients with T1 or T2 disease; [23, 61] two studies also included patients with T3 or higher stage disease (ranged from 0.83% to 2.3%).[24, 59, 60] In addition, three studies included patients who also received some form of ADTs (ranged from 17% to 39%). The methodological quality of two studies were rated B and two were rated C. Some of the deficiencies in these studies included failure to adjust for potential confounders and large proportion of patients (>20%) lost to follow-up.

Biochemical control or patient survival

None of the studies provided data on biochemical outcomes or patient survival.

Genitourinary toxicities (Tables C2-C3)

Four studies reported outcomes on adverse events of the genitourinary system using different disease specific quality of life instruments such as EPIC 26 and EPIC 50 [score ranged from 0 (worst) - 100 (best)] as well as the AUA symptom score (score ranged from 0 (best) - 35 (worst)). [23, 24, 59-61]

Two studies found worse urinary outcomes (e.g., increased urinary incontinence or obstruction) in the LDRBT arm compared with the EBRT arm. [23, 59, 60] The first study had a total sample size of 168 (N = 90 (LDRBT), N = 78 (EBRT)). [59, 60] The study reported worse outcomes in the LDRBT arm compared with EBRT arm (HR; 0.76 (95% CI 0.66 to 0.88), P <0.05). The second study had a total sample size of 598 (N=306 (LDRBT), N =292 (EBRT)). [23] The study found worse urinary incontinence and urinary irritation/obstruction in the LDRBT arm compared to the EBRT arm. A third study did not find significant difference between the two groups. [24]

The fourth study (N = 92 (LDRBT), N = 190 (EBRT)) stratified patients by baseline urinary function into normal, intermediate, and poor baseline function.[61] The study did not find any difference in urinary dysfunction between groups in patients with normal baseline function. Patients with intermediate baseline function had less urinary incontinence but more urinary obstruction/irritation in the LDRBT arm compared with patients in the EBRT arm. Patients with poor baseline function had more urinary obstruction/ irritation in the LDRBT arm compared with the EBRT arm.

Gastrointestinal toxicities (Tables C4-C5)

Four prospective studies that met our inclusion criteria reported gastrointestinal toxicities. [23, 24, 59-61] Three studies did not find significant difference in gastrointestinal toxicity rates between

groups,[23, 59-61] one study found lower rates of gastrointestinal toxicities in the LDRBT arm compared to the EBRT arm.[24]

Sexual dysfunction (Tables C6-7)

Four studies reported outcomes on sexual dysfunction using different disease specific quality of life instruments.[23, 24, 59-61] All except one[60] reported better outcomes in the LDRBT arm compared with the EBRT arm; it should be noted that in this study, 25.6% of patients in the LDRBT arm also received EBRT in addition to LDRBT.[60]

Retrospective studies (Table C8)

Nine retrospective cohorts compared LDRBT with EBRT.[17, 19-22, 25, 62-64] The sample size in these studies ranged from 233 to 133,904. Only one study included exclusively patients with T1 or T2 disease who did not receive any form of ADTs.[20] The other studies included some patients with T3 or higher stage disease (ranged from 4.3 % to 17.6%) and/or also received some form of ADTs (ranged from 20% to 30%).

Patient survival

Only one retrospective cohort study with a total sample size of 10,179 analyzed patient survival.[17] The study used the SEER staging to classify patients with local/regional prostate cancer into a localized disease category and other patients into a distant disease category. The analysis did not include any patients who received ADTs and adjusted for age, race, tumor stage, Gleason score, pretreatment comorbidity, and treatment modalities. The study directly compared BT and EBRT with no treatment or no initial treatment but did not directly compare BT with EBRT. However, the study provided sufficient data to allow for comparisons between BT and EBRT monotherapy [N = 644 (LDRBT), N = 876 (EBRT)]. Our calculations showed that there was no statistically significant difference between the two groups in the 7-year disease-specific survival rates [adjRR: 0.68 (95%CI, 0.30 to 1.5)]. The methodological quality this study was rated B.

Biochemical control (Figure C1)

Six studies reported outcomes of biochemical control using the Phoenix definition (PSA nadir plus 2 ng/mL),[19-22, 63, 64] in the form of biochemical No Evidence of Disease (bNED) or Freedom from Biochemical Failure (FFBF) at 5 years (except for one which reported FFBF at 4 years[20]). These studies all used different EBRT techniques such as 3D-CRT and IMRT in their analyses and some included patients who received a combination of treatment modalities.

Two studies exclusively included patients who did not receive ADTs. The first study reported statistically non-significant lower biochemical control rates in the LDRBT arm compared with EBRT arm (actuarial estimates 93.5% vs. 99.5%; P = 0.09). [20] The second study essentially found little or no difference in the biochemical control rates in the LDRBT arm compared with the EBRT arm (96% vs. 95%;).[19] The methodological quality of these studies were rated B.

Of the remaining four studies[21, 22, 63, 64] that included some patients who received ADTs, two[21, 22] found statistically significant results in favor of the LDRBT arm compared with the EBRT arm (95.2% vs. 84.7% ; P < 0.001;[21] 94% vs. 74%; P < 0.0001,[22] respectively). The third study reported higher biochemical control rates (81% vs. 64%; P <0.014),[63] in univariate analysis comparing LDRBT (with or without ADT) with EBRT (without ADT). After adjustment for pretreatment PSA concentration, the difference was no longer significant (P = 0.07). The fourth

study reported lower biochemical control rates (92%: 95 % CI, 86% to 96% vs. 93%; 95% CI, 86% to 97%) in the LDRBT arm compared with the EBRT arm (estimated risk difference: -0.01; 95% CI, -0.07 to 0.06).[64] The methodological quality of two studies were rated C and two were rated B. Common deficiencies in these studies include suboptimal reporting (e.g., discrepancies in reporting of results) and lack of adjustment for potential confounders.

Genitourinary toxicities (Table C2; Figure C2)

Three studies reported outcomes on acute or late genitourinary RTOG ≥ grade 3 toxicities.[20-22] The first study did not find statistical difference in the rate of acute genitourinary toxicities between LDRBT and EBRT (3.8% vs. 1.4%, P=0.176).[20] However, this study reported higher rate of late genitourinary toxicity in the LDRBT arm compared with the EBRT arm (5.6% vs. 0.5%, P <0.006). A second study reported the prevalence rate of late grade 3 or grade 4 genitourinary/gastrointestinal toxicity was higher in the LDRBT arm compared with the EBRT arm (5.3% vs. 1.8%).[21] The third study[22] provided individual data for 4 arms (LDRBT, EBRT-3D CRT, EBRT- IMRT, and LDRBT + EBRT) but did not analyze the comparison between LDRBT with EBRT; our own calculations showed that there was no significant difference in acute genitourinary toxicities between the LDRBT arm and EBRT arm (RD 0.02; 95% CI -0.00 to 0.04). However, those patients who received LDRBT had worse late genitourinary toxicities than patients who received EBRT (RD 0.06; 95% CI 0.30 to 0.10).

One study reported urethral strictures and found worse outcomes in the LDRBT arm compared with the EBRT arm (7% vs. 0%).[20] This result was statistically significant (RD 0.07; 95% CI 0.03 to 0.11).

Gastrointestinal toxicities (Table C4; Figure C2)

Four studies reported outcomes on acute or late gastrointestinal toxicities RTOG ≥ grade 3.[20-22, 62] Comparing LDRBT with EBRT, the first study found lower rates of acute (0% vs. 0.5%, respectively) and late gastrointestinal toxicities (0% vs. 2.8%, respectively) in the LDRBT group;[62] no statistical comparisons were reported specifically for the grade 3 or greater toxicity in this study. The second study found little or no difference in the rates of late gastrointestinal toxicities in the LDRBT arm compared with the EBRT arm (0.7% vs. 0%, P = 0.228).[20] We analyzed the results of the third study and did not find statistically significant difference between the two groups in acute and late gastrointestinal toxicities.[22] The fourth study reported that the prevalence rate of late grade 3 or grade 4 genitourinary/gastrointestinal toxicity was higher in the LDRBT arm compared with the EBRT arm (5.3% vs. 1.8%).[21]

Other adverse outcomes - incidence rate of bladder and rectal cancer (Tables C2, C4)

One retrospective cohort study analyzed the post-treatment incidence of bladder and rectal cancer in men who received LDRBT (N = 22,889) versus those who received EBRT (N = 93,059).[25] After more than 10 years of follow-up, the men in the LDRBT arm compared with men in the EBRT arm had lower rates of bladder (RR 0.72; 95% CI 0.59 to 0.87) and rectal cancer (RR 0.64; 95% CI 0.45 to 0.91). The methodological quality of this study was rated B.

Table C1. Characteristics of prospective cohort studies that compared LDRBT with EBRT

Author Year [UI] Country	Intervention or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobi-lization technique	Applied margins for PTV	Planning algorithm	Quality Comments
Chen 2009[19620493] USA	EBRT	190	69(51-82)	White 95 Black/other nd	100	<10: 67 10-20: 23 >20: 10	4-6: 48 7: 35 8-10: 18	nd	nd	nd	nd	nd	nd	C com-1
	BT	92	64(47-77)	White 91 Black/other nd	100	<10: 92 10-20 8 >20 0	4-6: 78 7:21 8-10: 1	nd	nd	nd	nd	nd	nd	
Ferrer 2008[18325680] Spain	EBRT	205	69.2 (5.5)	nd	98.0	10.1 (7.9)[A]	6.0 (1.1) [A]	33.7	74.03 (SD4.3)	1.8-2.0 daily; 5 d/wk	nd	1.01 cm (SD 0.18)	3D-treatment planning	B com-2 com-5
	LDRBT	275	66.9 (6.5)	nd	100	6.9(2.3) [A]	5.7(4.4) [A]	31.6	144 (D90 152 Gy; V100% =93%)	nd	nd	nd		
Litwin 2007 [17455209] Gore 2009[19509365] USA	EBRT	78	70.8 (7.3)	White 84.6 Non white 15.4	97.5	13.6 (21.6) [A]	6.7 (1.0) [A]	59	68-77	1.8-2.0 (90%-100% of the isodose line)	nd	nd	nd	C com-1
	LDRBT (74.4%) or BT with EBRT (25.6%); stratified by risk	90	68.4 (6.9)	White 78.9 Non white 21.1	97.8	10.6 (14.6) [A]	6.2 (0.8) [A]	23	nd on BT; 45 EBRT	nd	nd	nd	nd	
Sanda MG 2008 [18354103] USA	EBRT	292	69 (45-84)	White 82 Black 16 Other/not reported 3	100	<4: 16 4-10: 61 >10: 23	2-6: 44 7: 42 8-10: 14	30	nd	nd	nd	nd	nd	B com-5
	LDRBT	306	65 (44-84)	White 85 Black 12 Other/not reported 4	100	<4: 22 4-10: 71 >10: 7	2-6: 74 7: 25 8-10: 1	6	nd	nd	Transperineal technique.	nd	nd	

[A] Mean (standard deviation)
com-1: No adjustment for potential confounders
com-2: incomplete reporting (e.g., little or no description of study eligibility criteria or methods, missing data)
com-3: historical comparison
com-4: incomplete statistical analysis (e.g., P value not reported)

com-5: different lengths of follow-up between groups
com-6: baseline participant characteristics not entirely comparable between groups (no adjustment)
com-7: loss to follow-up ≥20% (only for RCTs)
com-8: method of randomization not reported

Table C2. Genitourinary toxicity: LDRBT vs. EBRT (qualitative)

Outcome	Interventions or comparisons (total sample size)	Findings		Quality
Prospective cohort studies				
Disease-specific QoL: urinary scores	LDRBT (N=715) vs. EBRT (N=695)	Sanda (2008)	Worse	B
		Ferrer (2008)	No diff	B
		Litwin (2007) or Gore (2009)	**Worse**[A]	C
		Chen (2009):		C
		- patients with normal function at baseline	No diff	
		- patients with intermediate function at baseline	Better / Worse[B]	
		- patients with poor function at baseline	Worse	
Retrospective cohort studies				
Acute GU ≥ Grade 3	LDRBT (N=383) vs. EBRT (N=800)	Eade (2008)	No diff	B
		Wong (2009)	No diff	B
Late GU ≥ Grade 3	LDRBT (N=383) vs. EBRT (N=800)	Eade (2008)	**Worse**	B
		Wong (2009)	**Worse**	B
Urethral strictures	LDRBT (N=158) vs. EBRT (N=216)	Eade (2008)	**Worse**	B
Incidence of bladder cancer (>10 years of follow-up)	LDRBT (N=22889) vs. EBRT (N=93059)	Nieder (2008)	**Better**	B

Better: net difference in urinary scores improved >1 point or statistically significant risk difference in increasing acute/late GU toxicity or other adverse outcomes, comparing LDRBT with EBRT

No diff: net difference in urinary scores within 1 point or no statistically significant risk difference in acute/late GU toxicity and other adverse outcomes, comparing LDRBT with EBRT

Worse: net difference in urinary scores worsen >1 point or statistically significant risk difference in decreasing acute/late GU toxicity or other adverse outcomes, comparing LDRBT with EBRT

Bold words signify statistical significance P<0.05

[A] Based on the Hazard Ratio of returning to baseline UCLA urinary score comparing the two groups

[B] Better for urinary incontinence score, and worse for urinary obstruction or irritation score

Table C3. Urinary dysfunction scores: LDRBT vs. EBRT

Author Year [UI] Country	Outcome	Intervention	Follow up, yr	No. Analyzed	Baseline	Change (SD)	Net diff	95% CI	P btw	Quality
Sanda 2008 [18354103] USA	EPIC-26 urinary incontinence score	LDRBT	1	272	94[A]	-7 (nd)	-6	nd	nd	B
		EBRT	1	258	92[A]	-1 (nd)				
	EPIC-26 urinary irritation or obstruction score	LDRBT	1	272	90[A]	-8 (nd)	-11	nd	nd	
		EBRT	1	258	87[A]	+3 (nd)				
Ferrer 2008 [18325680] Spain	EPIC-50 urinary score	LDRBT	2	275	95.2	+2.8 (12)	-0.60	-2.63, 1.43	NS	B
		EBRT	2	205	96.4	+2.2 (10)				
Litwin 2007 [17455209] Gore 2009 [19509365] USA	UCLA PCI urinary score	LDRBT (74.4%) or BT with EBRT (25.6%)	2	90	90[A]	-8 (nd)	HR: 0.76	0.66, 0.88	<0.05[B]	C
		EBRT	2	78	93[A]	-3 (nd)				
	AUA symptom index	LDRBT (74.4%) or BT with EBRT (25.6%)	2	90	10[A]	+3 (nd)	HR: 0.68	0.61, 0.78	<0.05[C]	
		EBRT	2	78	10[A]	-1 (nd)				
Chen 2009 [19620493] USA	PCSI urinary incontinence score	BT	3	70 8	Normal: 0 Intermediate: 28.9	+5.4 (nd) -13.8 (nd)	-0.1 -11.7	nd nd	nd nd	C
		EBRT	3	120 34	Normal: 0 Intermediate: 30.5	+5.5 (nd) -2.1 (nd)				
	PCSI urinary obstruction or irritation score	BT	3	36 26 13	Normal: 9.0 Intermediate: 21.4 Poor: 29.4	+5.7 (nd) -2.4 (nd) -3.4 (nd)	-0.6 -2.5 +4.1	nd nd nd	nd nd nd	
		EBRT	3	51 63 38	Normal: 9.2 Intermediate: 21.3 Poor: 36.2	+6.3 (nd) +0.3 (nd) -7.5 (nd)				

Diff, difference; PCSI, Prostate Cancer Symptom Indices (range, 0-100) in which higher scores indicate worse outcomes; EPIC, Expanded Prostate Cancer Index Composite (range, 0-100) in which higher scores indicate better outcomes; UCLA PCI, University of California – Los Angeles Prostate Cancer Index (range, 0-100) in which higher scores indicate better outcomes; AUA symptom index, American Urological Association symptom index (range, 0-35) in which higher scores indicate worse outcomes

[A] Estimated value from the figure
[B] Based on the Hazard Ratio of returning to baseline UCLA urinary score comparing the two groups
[C] Based on the Hazard Ratio of returning to baseline AUA symptom index comparing the two groups

Table C4. Gastrointestinal toxicity: LDRBT vs. EBRT (qualitative)

Outcome	Interventions or comparisons (total sample size)	Study	Findings	Quality
Prospective cohort studies				
Disease-specific QoL: bowel scores	LDRBT (N=709) vs. EBRT (N=681)	Sanda (2008)	No diff	B
		Ferrer (2008)	**Better**[A]	B
		Litwin (2007) or Gore (2009)	No diff[B]	C
		Chen (2009)	Better	C
Retrospective cohort studies				
Acute GI ≥ Grade 3	LDRBT (N=275) vs. EBRT (N=767)	Wong (2009)	No diff	C
		Lesperance (2008)	No diff	C
Late GI ≥ Grade 3	LDRBT (N=433) vs. EBRT (N=979)	Eade (2008)	No diff	B
		Wong (2009)	No diff	B
		Lesperance (2008)	No diff	C
Incidence of rectal cancer (>10 years of follow-up)	LDRBT (N=22889) vs. EBRT (N=93059)	Nieder (2008)	**Better**	B

Better: net difference in urinary scores improved >1 point or statistically significant risk difference in increasing acute/late GI toxicity or other adverse outcomes, comparing LDRBT with EBRT

No difference: net difference in urinary scores within 1 point or no statistically significant risk difference in acute/late GI toxicity and other adverse outcomes, comparing LDRBT with EBRT

Worse: net difference in urinary scores worsen >1 point or statistically significant risk difference in decreasing acute/late GI toxicity or other adverse outcomes, comparing LDRBT with EBRT

Bold words signify statistical significance P<0.05

[A] Adjusted for pretreatment score, age at diagnosis, risk group and hormonal treatment using generalized equation models

[B] Based on the Hazard Ratio of returning to baseline UCLA bowel score comparing the two groups

Table C5. Bowel dysfunction scores: LDRBT vs. EBRT

Author Year [UI] Country	Outcome	Intervention	Follow up, yr	No. Analyzed	Baseline	Change (SD)	Net diff	95%CI	P btw	Quality
Sanda 2008 [18354103] USA	EPIC-26 bowel or rectal score	LDRBT	1	272	96[A]	-4 (nd)	0	nd	nd	B
		EBRT	1	258	94[A]	-4 (nd)				
Ferrer 2008 [18325680] Spain	EPIC-50 bowel score	LDRBT	2	275	96.9	+1.0 (5.9)	3.6	2.04, 5.16	<0.05[B]	B
		EBRT	2	205	97.1	-2.6 (11)				
Litwin 2007 [17455209] Gore 2009 [19509365] USA	UCLA PCI bowel score	LDRBT (74.4%) or BT with EBRT (25.6%)	2	90	84[A]	-5 (nd)	HR: 0.91	0.83, 1.01	NS[C]	C
		EBRT	2	78	85[A]	-5 (nd)				
Chen 2009 [19620493] USA	PCSI bowel problem	BT	3	42 30	Normal: 0 Intermediate: 7.5	+5.4 (nd) +1.9 (nd)	-1.1 -2.1	nd nd	nd nd	C
		EBRT	3	64 76	Normal: 0 Intermediate: 6.8	+6.5 (nd) +4.0 (nd)				

Diff, difference; PCSI, Prostate Cancer Symptom Indices (range, 0-100) in which higher scores indicate worse outcomes; EPIC, Expanded Prostate Cancer Index Composite (range, 0-100) in which higher scores indicate better outcomes; UCLA PCI, University of California – Los Angeles Prostate Cancer Index (range, 0-100) in which higher scores indicate better outcomes

[A] Estimated value from the figure
[B] Adjusted for pretreatment score, age at diagnosis, risk group, and hormonal treatment using generalized estimating equations models
[C] Based on the Hazard Ratio of returning to baseline UCLA bowel score comparing the two groups

Table C6. Sexual Dysfunction: LDRBT vs. EBRT (qualitative)

Author Year [UI] Country	Outcome	Intervention	Follow -up, yr	No. Analyzed	Net function: better, no diff, or worse	P btw	Quality
Sanda 2008 [18354103] USA	EPIC-26 sexual score	LDRBT	1	272	Better	nd	B
		EBRT	1	258			
Ferrer 2008 [18325680] Spain	EPIC-50 sexual score	LDRBT	2	275	**Better**	<0.05[A]	B
		EBRT	2	205			
Litwin 2007 [17455209]	UCLA PCI sexual score	LDRBT (74.4%) or BT with EBRT (25.6%)	2	90	**Worse**	<0.05[B]	C
Gore 2009 [19509365] USA		EBRT	2	78			
Chen 2009 [19620493] USA	PCSI sexual dysfunction score	BT	3	26 29 20	Better Better Better	nd nd nd	C
		EBRT	3	31 39 80			

PCSI, Prostate Cancer Symptom Indices (range, 0-100) in which higher scores indicate worse outcomes; EPIC, Expanded Prostate Cancer Index Composite (range, 0-100) in which higher scores indicate better outcomes; UCLA PCI, University of California – Los Angeles Prostate Cancer Index in which higher scores indicate better outcomes
Better: net difference in function scores improved >1 point
No diff: net difference in function scores within 1 point
Worse: net difference in function scores worsen >1 point
Bold words signify statistical significance P<0.05

Adjusted for pretreatment score, age at diagnosis, risk group, and hormonal treatment using generalized estimating equations models
Based on the Hazard Ratio of returning to baseline UCLA PCI sexual score comparing the two groups

Table C7. Sexual dysfunction scores: LDRBT vs. EBRT

Author Year [UI] Country	Outcome	Intervention	Follow up, yr	No. Analyzed	Baseline	Change (SD)	Net diff	95%CI	P btw	Quality
Sanda 2008 [18354103] USA	EPIC-26 sexual score	LDRBT	1	272	67[A]	-6 (nd)	+4	nd	nd	B
		EBRT	1	258	62[A]	-10 (nd)				
Ferrer 2008 [18325680] Spain	EPIC-50 sexual score	LDRBT	2	275	48.6	+1.2 (21)	+7.9	3.5, 12.3	<0.05[B]	B
		EBRT	2	205	50.2	-6.7 (28)				
Litwin 2007 [17455209] Gore 2009 [19509365] USA	UCLA PCI sexual score	LDRBT (74.4%) or BT with EBRT (25.6%)	2	90	40[A]	-10 (nd)	HR: 0.82	0.69, 0.97	<0.05[C]	C
		EBRT	2	78	40[A]	-12 (nd)				
Chen 2009 [19620493] USA	PCSI sexual dysfunction score	BT	3	26	Normal: 1.9	+18.8 (nd)	-21.4	nd	nd	C
				29	Intermediate: 23.7	+32.1 (nd)	-6.9	nd	nd	
				20	Poor: 73.8	-0.8 (nd)	-4.3	nd	nd	
		EBRT	3	31	Normal: 2.1	+40.2 (nd)				
				39	Intermediate: 25.8	+39.0 (nd)				
				80	Poor: 80.7	+3.5 (nd)				

Diff, difference; PCSI, Prostate Cancer Symptom Indices (range, 0-100) in which higher scores indicate worse outcomes; EPIC, Expanded Prostate Cancer Index Composite (range, 0-100) in which higher scores indicate better outcomes; UCLA PCI, University of California – Los Angeles Prostate Cancer Index in which higher scores indicate better outcomes

[A] Estimated value from the figure

[B] Adjusted for pretreatment score, age at diagnosis, risk group, and hormonal treatment using generalized estimating equations models

[C] Based on the Hazard Ratio of returning to baseline UCLA PCI sexual score comparing the two groups

Table C8. Characteristics of retrospective cohort studies that compared LDRBT with EBRT

Author Year [UI] Country	Intervention or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobi-lization technique	Applied margins for PTV	Planning algorithm	Quality Comments
Eade 2008[18207665] USA	EBRT	216	67.6 (26.7-80.6)	nd	100	5.2 (0.4-9.6)[A]	≤6: 100	0	74-78	2.0 daily	α-cradle (Smithers Med Prod, Inc.) for simulation	0.5-0.6 cm posterior; 0.8 cm all other directions	Step-and-shoot inverse planning (Corvus)	B
	LDRBT	158	64.7 (42.0-78.3)	nd	100	5.2 (0.5-9.8)[A]	≤6: 100	0	145 (8 pts had 160)	nd	nd	0.3-0.5 cm	Variseed software (Varian)	
Gondi 2007[17382161] USA	BT +/ EBRT +/ ADT	72 (21 BT alone, 51 with EBRT,)	nd	nd	100	≤10 75 >10 25	2-6: 26 7: 74	11 ADT 12 EBRT+ ADT	66-70.6 Gy (ASTRO)	nd	nd	1cm margins	nd	C com-2
	SD-EBRT No ADT	141	nd	nd	100	≤10: 74 >10: 26	2-6: 52 7: 48	nd	45Gy + BT boost after EBRT		nd	nd	nd	
	SD EBRT with ADT	84	nd	nd	100	≤10: 55 >10: 45	2-6: 20 7: 80	nd		nd	nd	nd	nd	
Jabbari S 2010[19409729] USA	LDRBT (57% BT alone, 7% EBRT,) low risk subset	134	63 (43-78)	nd	100	5.9: (0.4-9.7)[A]	<6: 100 7: 0 8-10: 0	31 ADT 5 ADT +EBRT	144Gy for I-125 or 125 Gy for pd	nd	nd	nd	nd	C com-5

Author Year [UI] Country	Intervention or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobi-lization technique	Applied margins for PTV	Planning algorithm	Quality Comments
	EBRT (100% EBRT) Low risk subset	124	70 (55-86)	nd	100	6.4: (0.4-9.5)[A]	<6: 100 7: 0 8-10: 0		63-79	1.8 Gy	Static field conformal technique	nd	Preoperative forward planning	
	LDRBT (47% BT alone, 12% EBRT,)	206	63 (43-78)	nd	100	6.3: (0.4-14.7)[A]	<6: 83.5 7: 16 8-10: 0.5	28 ADT 13 ADT + EBRT	nd	nd	nd	nd		
Lesperance 2008[18374892] USA	EBRT	183	68.2 (48-84)	White 66.6 Black 23 Other 10.4	76	nd	5-7: 79 8-10: 19	38	64-76	1.8	nd	nd	Treatment planning CT	C com-6
	LDRBT	50	63 (47-98)	White 72 Black 16 Other 12	96	nd	5-7: 82 8-10: 2	16	(12 pts received 46 Gy EBRT boost)	nd	nd	nd	nd	
Nieder 2008[18801517] USA	EBRT	93059	40-49: 0.65 50-59: 7.46 60-69: 31.93 70-79: 52.56 80+: 7.40	White 81.59 Black 12.51 Other 5.91	51.23	nd	2-4: 9 5-7: 64.01 8-10: 22.47 Unknown: 4.53	nd nd	nd	nd	nd	nd	nd	B

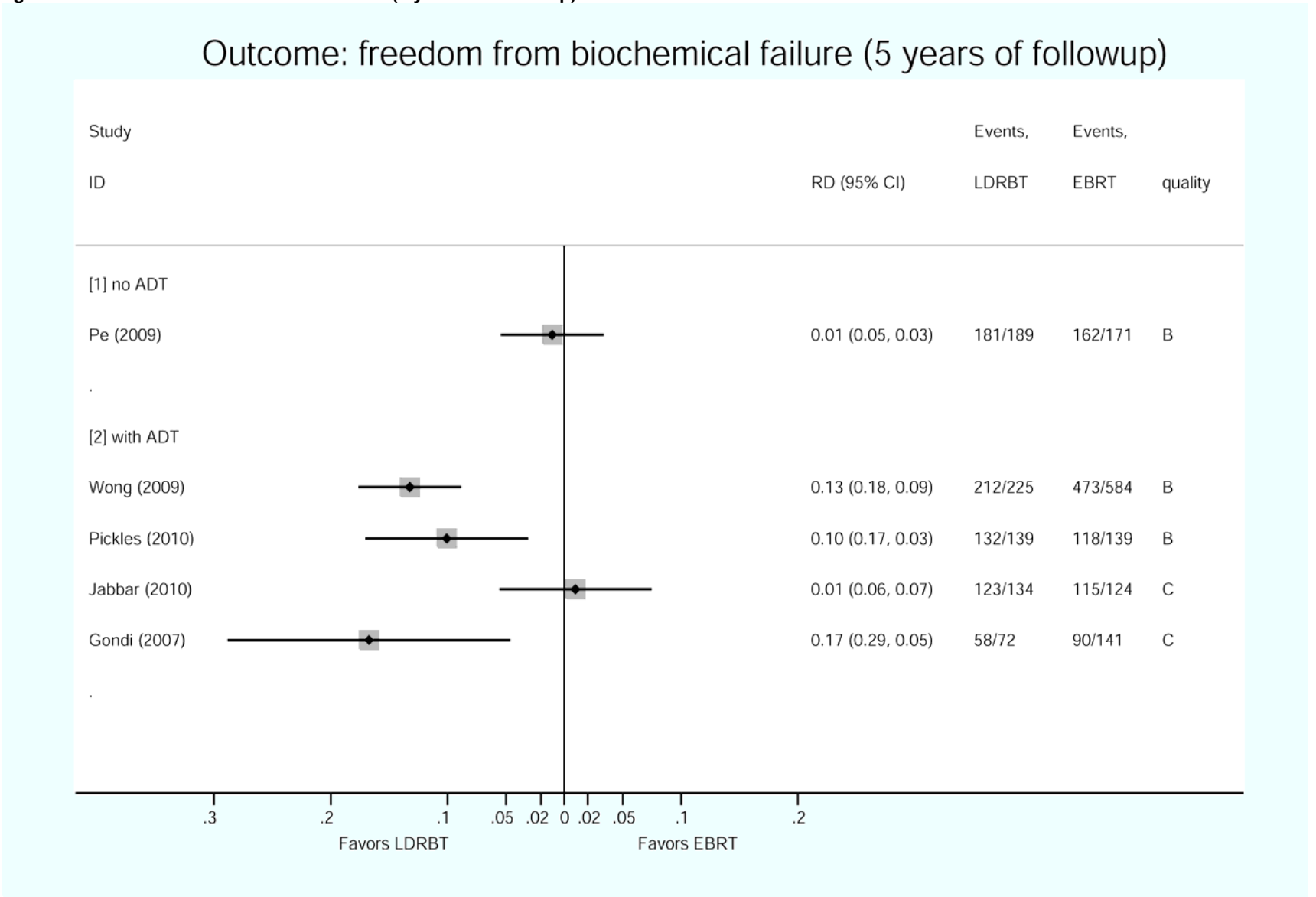
Author Year [UI] Country	Intervention or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobi-lization technique	Applied margins for PTV	Planning algorithm	Quality Comments
	LDRBT	22889	40-49: 1.28 50-59: 16.12 60-69: 41.10 70-79: 38.28 80+: 3.22	White 88.17 Black 8.42 Other 3.41	62.87	nd	2-4: 5.84 5-7: 83.52 8-10: 7.04 Unknown: 3.6		nd	nd	nd	nd	nd	
	EBRT + LDRBT	17956	40-49: 1.50 50-59: 15.52 60-69: 39.94 70-79: 40.08 80+: 2.96	White 82.33 Black 13.77 Other 3.90	57.31	nd	2-4: 4.96 5-7: 69.22 8-10: 22.64 Unknown: 3.17	nd	nd	nd	nd	nd	nd	
Pe ML 2009 [19376564] USA	EBRT	189	70(49-83)	White 77.7 Black 18.3 Other 4.1	100	6.5: (0.6-9.9)[A]	nd	0	73.8	nd	nd	nd	nd	B
	LDRBT	171	65(42-78)	White 85 Black 9.3 Other 5.2	100	5.7: (0.8-9.8)[A]	nd	0	145	nd	nd	3-5mm	nd	
Pickles T 2010[19570619] Canada	EBRT	139	71 (54-84)	nd	100	5.6[A]	2-6: 87.87: 12.2	30.231.7	55.2-72	nd	nd	1–1.5 cm	CT imaging without daily image guidance	B

Author Year [UI] Country	Intervention or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobi-lization technique	Applied margins for PTV	Planning algorithm	Quality Comments
	LDRBT	139	64 (48-79)	nd	100	6.4[A]	2-6: 87.8 7: 12.2		144	nd	nd	nd	real-time 0.33 mCi (NIST99) of I-125 sources (model 6711; (Oncura)	
Wong 2009[19670452] USA	EBRT(3D CRT)	270	nd		90	≤10: 71 10.1-20: 19 ≥20: 10	≤6: 65	28	45 Gy	1.8 to 2	nd	1.0 to 2.0 cm	none	B
	EBRT(IMRT)	314	nd		96	≤10: 76 10.1-20: 17 ≥20: 7	≤6: 44		Median dose of 75.6 Gy	nd	nd	6 to 10 mm	CT	
	LDRBT	225	nd		100	≤10: 86 10.1-20: 12 ≥20: 2	≤6: 77	32	144 Gy for I-125 and 120 Gy for pd-103	n/a	nd	n/a	nd	
	EBRT+LDRBT	44	nd		98	≤10: 65 10.1-20: 30 ≥20: 5	≤6: 45	27	45 Gy	nd	nd	nd	nd	
Zhou EH 2009[18538495] USA	EBRT	876		White or other 90.1 Black 9.9		nd	<7: 76.9 7-10: 15.4 Unknown: 7.7	0	nd	nd	nd	nd	nd	B com-1
	BT	644		White or other 94.5 Black 5.5		nd	<7: 82.4 7-10: 8.2 Unknown: 9.4	0	nd	nd	nd	nd	nd	

Author Year [UI] Country	Intervention or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobi-lization technique	Applied margins for PTV	Planning algorithm	Quality Comments
	NT	2306		White or other 89.3 Black 10.6		nd	<7: 70.12 7-10: 14.6 Unknown: 15.3	0	nd	nd	nd	nd	nd	

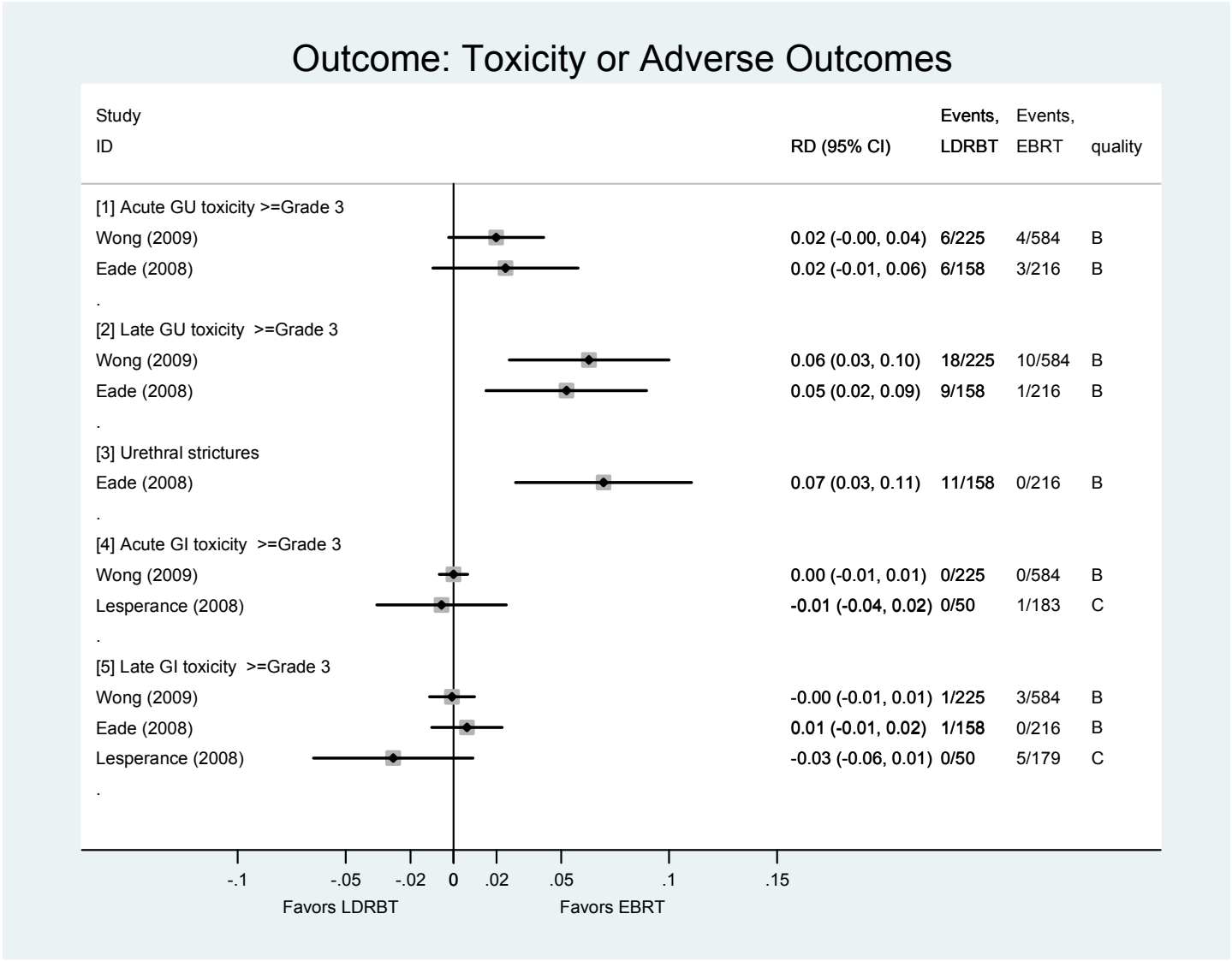
A Median (range)
com-1: No adjustment for potential confounders
com-2: incomplete reporting (e.g., little or no description of study eligibility criteria or methods, missing data)
com-3: historical comparison
com-4: incomplete statistical analysis (e.g., P value not reported)
com-5: different lengths of follow-up between groups
com-6: baseline participant characteristics not entirely comparable between groups (no adjustment)
com-7: loss to follow-up ≥20% (only for RCTs)
com-8: method of randomization not reported
nd: no data provided

Figure C1. Freedom from biochemical failure (5 years of follow-up): LDRBT vs. EBRT



*Gondi (2007) comparing BT (with or without ADT) with EBRT (without ADT).

Figure C2. Genitourinary and gastrointestinal toxicity: LDRBT vs. EBRT*



*Studies that reported continuous outcomes for GU and GI toxicity (e.g., urinary score and bowel score) are not included in this figure. The detailed results for these studies are summarized in Tables C3 and C5.

LDRBT vs. HDRBT (Table C9; Figure C3)

We did not identify any eligible RCTs or prospective cohort studies for this comparison. One retrospective study reported the combined experience from 2 centers comparing HDR using Ir-192 (38 Gy or 42 Gy) with LDR using Pd-103 (120 Gy).[26] A total of 454 participants were evaluated. All had either T1 or T2 disease. Up to one-third of the participants had some form of ADTs. There was no difference in the 5-year freedom from biochemical failure in the two groups (88% in HDR vs. 89% in LDR; P = 0.62). In terms of morbidity comparing HDR with LDR, acute (< 6 months) genitourinary toxicity ≥ grade 3 was 4.5% versus 14.5%; for chronic (> 6 months) genitourinary toxicity ≥ grade 3, it was 9% versus 8.5%; for acute gastrointestinal toxicity ≥ grade 3, it was 0% versus 0.5%; and for chronic gastrointestinal toxicity, it was 0.5% versus 2%. No P values were provided for these comparisons. The proportion of patients with impotency at 5 years did not differ between groups (20% in HDR vs. 30% in LDR; P = 0.23). It should be noted that the treatment techniques evolved over time in the two groups. The methodological quality of this study was rated C because there was no statistical adjustment for potential confounders.

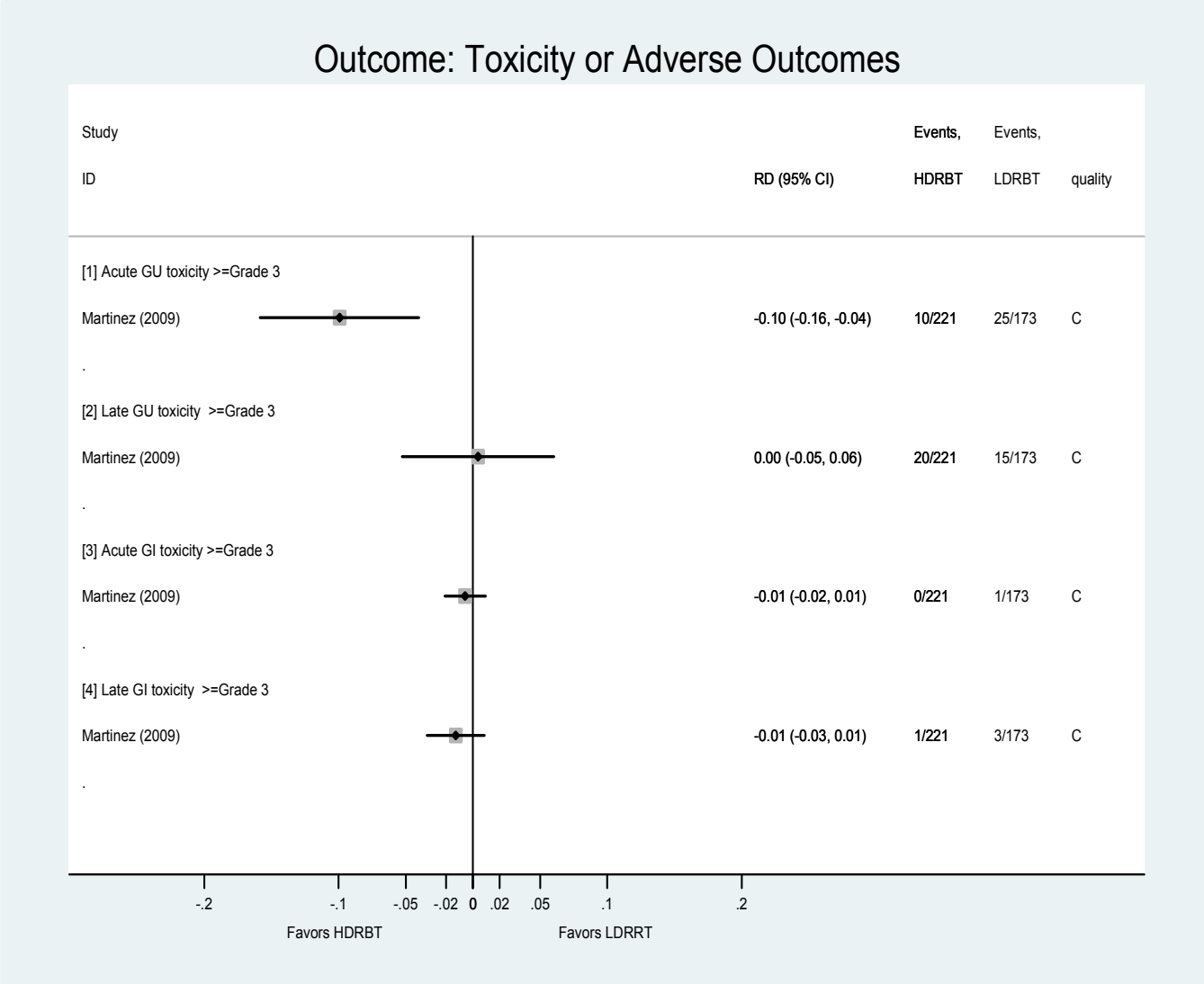
Table C9. Characteristics of retrospective cohort studies that compared HDRBT with LDRBT

Author Year [UI] Country	Intervention(s) or comparison	N	Mean age, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobilization technique	Applied margins for PTV	Planning algorithm	Quality Comments
Martinez 2009 [19952715] US	HDRBT (Ir-192) [A]	259	64	nd	100	≤3.9: 16 4-9.9: 80 >10: 4 [B]	≤5 8 6 83 >7 9	27	38; 42	9.5; 7	nd	150% isodose line not touching urethra	U/S or real time (Oncentra-prostate)	C com-1
	LDRBT (Pd^{103}) [B]	206	66	nd	100	≤3.9: 19 4-9.9: 76 >10: 5	≤5 18 6 75 >7 7	31	120	nd	nd	nd	U/S or real time (Oncentra-prostate)	

A estimated, discrepancy in CET data in Table 1 in paper
B procedure evolved over the study years; 2 centers had different procedures

com-1: No adjustment for potential confounders
com-2: incomplete reporting (e.g., little or no description of study eligibility criteria or methods, missing data)
com-3: historical comparison
com-4: incomplete statistical analysis (e.g., P value not reported)
com-5: different lengths of follow-up between groups
com-6: baseline participant characteristics not entirely comparable between groups (no adjustment)
com-7: loss to follow-up ≥20% (only for RCTs)
com-8: method of randomization not reported

Figure C3. Genitourinary and gastrointestinal toxicity: HDRBT vs. LDRBT



Appendix D. Detailed results for the comparisons in combination therapies

Combination Therapies: LDRBT plus EBRT in different doses (Tables D1-D5)

Randomized controlled trials (RCTs) (Tables D1)

One RCT, enrolling a total of 159 patients, compared LDRBT plus 20 Gy of EBRT (N = 83) against LDRBT plus 44 Gy of EBRT (N = 76), with 23% and 41% of patients receiving some form of ADTs, respectively.[27] This study enrolled only patients with T1c-T2a cancer, and the methodological quality of the study was rated B.

Biochemical failure

There was no significant difference in the 3-year actuarial freedom from biochemical failure rate between the two arms, with respective failure rates of 83% and 88% (P = 0.64).

Prospective studies

There were no prospective studies comparing LDRBT versus EBRT in different doses for the treatment of localized prostate cancer that met our inclusion criteria.

Retrospective studies

There were no retrospective studies comparing LDRBT versus EBRT in different doses for the treatment of localized prostate cancer that met our inclusion criteria.

Combination Therapies: EBRT vs. EBRT plus HDRBT (Tables D1-D5, Figure D1)

Randomized controlled trials (RCTs) (Table D1)

One RCT, enrolling a total of 104 patients, compared EBRT (N = 53) against EBRT plus HDRBT (N = 51).[28] No patients received ADTs, 40% of patients in this study had T3-T4 cancer. The methodological quality of this study was rated B.

Biochemical failure

There was no significant difference in biochemical failure rates between the two arms, after a mean follow-up period of 8.2 years. The failure rate of the EBRT arm was 83%, compared to 88% for the EBRT plus HDRBT arm (P = 0.37).

Prospective studies (Table D2)

One prospective study, enrolling a total of 97 patients, compared EBRT (N = 57) against EBRT plus HDRBT (N = 40).[65] Up to 11% of patients had T3 or T4 cancer and 36.8% of patients in the EBRT arm and 42.5% of patients in the EBRT plus HDRBT arm received some form of ADTs. This study was rated C because of unclear study description and suboptimal reporting of results.

Genitourinary toxicity (Table D4, Figure D1)

No patients in the EBRT plus HDRBT arm experienced grade 3 or grade 4 genitourinary toxicity, while 1.7% of patients in the EBRT arm did. No P values were reported for this comparison.

Gastrointestinal toxicity (Table D5, Figure D1)

No patients in the EBRT plus HDRBT arm experienced grade 3 or grade 4 gastrointestinal toxicity, while 8.8% of patients in the EBRT arm did. No P values were reported by the study investigators, our own calculation showed a P value of 0.15.

Retrospective studies (Table D3)

One study enrolled a total of 111 patients, with 10% of patients having T3 or T4 cancer in the EBRT arm (N = 88), compared to 17% in the EBRT plus HDRBT arm (N = 23).[30] Data on the proportion of patients receiving ADTs was not reported. The methodological quality of this study was rated B.

Quality of life

No significant difference was found between the EBRT and EBRT plus HDRBT arms with respect to health-related quality of life after one year, utilizing a modified Functional Assessment of Cancer Therapy-Prostate (FACT-P) survey instrument. A higher total score on the FACT-P scale indicates a better overall quality of life. Patients in the EBRT arm had a mean score of 97.64, while patients in the EBRT plus HDRBT arm had a mean score of 95.04 (P = 0.668).

Combination Therapies: EBRT plus LDRBT vs. EBRT plus HDRBT (Tables D2; D4-D5, Figure D1)

Randomized controlled trials (RCTs)

There were no RCTs comparing EBRT plus LDRBT versus EBRT plus HDRBT for the treatment of localized prostate cancer that met our inclusion criteria.

Prospective studies (Tables D2, D6)

One study enrolled a total of 110 patients, with 49 patients in the EBRT plus HDRBT group and 61 in the EBRT plus LDRBT group.[29] There were no data on the proportion of patients with stage T3/T4 cancer or the proportion who received some form of ADTs. The methodological quality of this study was rated B. It was unclear how many patients were eligible for the study but not included in the analysis.

Genitourinary toxicity (Table D4, Figure D1)

No significant difference was found in the Prostate Symptom Self Report (PSSR) Urinary Score after one year. The PSSR has a range from 0-100, in which higher scores indicate worse symptoms. It measures the frequency, severity, bothersomeness, and quality of urinary, bowel, and sexual symptoms experienced during the past month. Patients in the EBRT plus LDRBT group had a mean increase of 8.98 from baseline, while those in the EBRT plus HDRBT group had a mean increase of 2.79 from baseline (our calculation showed a P value of 0.10).

Gastrointestinal toxicity (Table D5, Figure D1)

No significant difference was found in the PSSR Bowel Score after one year. Patients in the EBRT plus LDRBT group had a mean increase of 4.73 from baseline, while those in the EBRT plus HDRBT group had a mean increase of 5.25 from baseline (P = 0.85).

Sexual dysfunction

No significant difference was found in PSSR Sexual Score after one year. Patients in the EBRT plus LDRBT group had a mean increase of 10.72 from baseline, while those in the EBRT plus HDRBT group had a mean increase of 9.61 from baseline (P = 0.77).

Retrospective studies

There were no retrospective studies comparing EBRT plus LDRBT versus EBRT plus HDRBT in different doses for the treatment of localized prostate cancer that met our inclusion criteria.

Combination Therapies: LDRBT vs. LDRBT plus EBRT (Tables D3-D6, Figure D1)

Randomized controlled trials (RCTs)

There were no RCTs comparing LDRBT versus LDRBT plus EBRT for the treatment of localized prostate cancer that met our inclusion criteria.

Prospective studies

There were no prospective studies comparing LDRBT versus LDRBT plus EBRT for the treatment of localized prostate cancer that met our inclusion criteria.

Retrospective studies (Table D3)

There were two retrospective studies comparing LDRBT versus LDRBT plus EBRT for the treatment of localized prostate cancer that met our inclusion criteria. One enrolled a total of 30 patients, with 15 in each group and none of whom had T3/T4 cancer, with no data on ADT treatment[66] The methodological quality of this study was rated C. This study had different selection criteria for the different comparison arms and there was no adjustment for potential confounders.

Another study enrolled a total of 343 patients.[67] In the LDRBT arm [N = 216], no patients had T3/T4 cancer, and 1% had been treated with ADT. In the LDRBT plus EBRT arm [N = 127], 2% of patients had T3/T4 cancer, and 34% had been treated with ADT. The methodological quality of this study was rated C. Baseline characteristics between groups were not entirely comparable; there was no adjustment for potential confounders.

Genitourinary toxicity (Table D4, D6, Figure D1)

First study reported no significant difference in the International Prostate Symptom Score (IPSS) score after 4 months between the two arms.[66] In the IPSS, a higher score indicate increased dysfunction. Patients in the LDRBT arm had a mean score of 9.5, while those in the LDRBT plus EBRT arm had a mean score of 12.0 (P = 0.39).

In the second study, 6% of the LDRBT group had acute urinary toxicity of grade 3 or grade 4 and none had late urinary toxicity of grade 3 or grade 4, while 2% of the LDRBT plus EBRT group had acute urinary toxicity and 1% had late urinary toxicity[67] P-values were not provided for the comparison.

Gastrointestinal toxicity (Table D5, Figure D1)

One study reported no patients as having either acute rectal toxicity of grade 3 or grade 4 or late rectal toxicity of grade 3 or grade 4.[67]

Combination Therapies: EBRT plus BT vs. No Radiotherapy, EBRT, or BT (Tables D3-D4)

In this comparison, BT refers to brachytherapy in general, i.e., studies that did not specify the type of brachytherapy.

Randomized controlled trials (RCTs)

There were no RCTs examining this particular comparison that met our inclusion criteria.

Prospective studies

There were no prospective studies examining this particular comparison that met our inclusion criteria.

Retrospective studies (Table D3)

There were two retrospective studies comparing EBRT plus BT versus no treatment or no initial treatment for the treatment of localized prostate cancer that met our inclusion criteria. Both studies analyzed SEER data. One study evaluated 231 patients in the EBRT plus BT group and 378 in the no radiotherapy group.[18] Two percent of patients had T3/T4 cancer, and no data was reported on the proportion of patients who had ADTs. The methodological quality of this study was rated as B.

Another study evaluated 9,096 patients in the EBRT plus BT group and 40,733 in the no radiotherapy or surgery group, with 20.5% of patients having T3/T4 cancer in the EBRT + BT arm, and 21.9% in the no radiotherapy or surgery arm.[14] There were no data on the proportion of patients who had ADTs. The methodological quality of this study was rated B.

Genitourinary toxicity (Table D4)

One study reported a significantly higher incidence of urethral strictures in the BT + EBRT arm than in the EBRT arm at a median follow-up of 2.7 years. 5.2% of patients in the BT + EBRT arm had urethral strictures, compared to 1.7% in the EBRT arm.[18]

Second primary cancer (Table D4)

One study reported on the incidence of second primary cancers in patients treated with EBRT and in patients treated with combination EBRT plus BT.[14] The study did not directly compare the two groups. Our own calculation showed the incidence of second primary cancers to be significantly greater in the EBRT group compared to the EBRT plus BT group (10.3% vs. 5.7%; OR 1.9, 95%CI, 1.7 to 2.1). Our own calculation also showed the incidence of late second primary cancers to be significantly greater in the EBRT group compared to the EBRT plus BT group (4.2% vs. 1.4%; OR 3.0, 95%CI, 2.5 to 3.6).

Combination Therapies: EBRT (3D-CRT) plus LDRBT vs. LDRBT, or EBRT (3D-CRT), or EBRT (IMRT) (Tables D3-D5, Figure D1)

In this comparison, BT refers to brachytherapy in general, i.e., studies that did not specify the type of brachytherapy.

Randomized controlled trials (RCTs)

There were no RCTs examining this particular comparison that met our inclusion criteria.

Prospective studies

There were no prospective studies examining this particular comparison that met our inclusion criteria.

Retrospective studies (Table D3)

There was one retrospective study comparing EBRT (3D-CRT) plus LDRBT [N= 44] versus LDRBT [N = 225], EBRT (3D-CRT) [N = 270], or EBRT (IMRT) [N = 314] for the treatment of localized prostate cancer that met our inclusion criteria.[22] Ninety percent of patients had stage T1 or T2 disease in the EBRT arm, compared to 98% in the EBRT plus HDRBT arm. Data on the proportion of patients who had ADTs was not reported. The methodological quality of this study was rated B.

Biochemical control

As the study did not directly compare LDRBT plus EBRT against EBRT or LDRBT, our own analysis showed no significant difference in 5-year biochemical control in these two comparisons (P = 0.142 and P = 0.8, respectively). Patients in the LDRBT plus EBRT arm had a control rate of 94%, while those in the EBRT arm had a rate of 87% and those in the LDRBT arm had a rate of 94%.

Genitourinary toxicity (Table D4, Figure D1)

Our analysis showed no significant difference in acute grade 3 genitourinary toxicity when comparing LDRBT plus EBRT against EBRT (P = NS), nor was there a significant difference found when comparing LDRBT plus EBRT against LDRBT (P = NS). There was a significant difference found in late grade 3 genitourinary toxicity when comparing LDRBT plus EBRT against EBRT ($P < 0.05$), but there was not a significant difference found when comparing LDRBT plus EBRT against LDRBT (P = NS).

Gastrointestinal toxicity (Table D5, Figure D1)

Our analysis showed no significant difference in either acute or late grade 3 gastrointestinal toxicity when comparing LDRBT plus EBRT against EBRT or when comparing LDRBT plus EBRT against LDRBT (P = NS).

Table D1. Characteristics of randomized controlled trials that compared combinations of radiotherapies with EBRT or LDRBT

Author Year [UI] Country	Intervention(s) or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobilization technique	Applied margins for PTV	Planning algorithm	Quality Comments
Sathya 2005 15718316 Canada	EBRT	53	66	nd	60%	20.2	2-6: 34% 7: 53% 8-10: 13%	0%	66 Gy in 33 fractions	2 Gy/fraction	nd	nd	nd	B
	HDRBT + EBRT	51	65	nd	61%	19.0	2-6: 37% 7: 45% 8-10: 18%	0%	IM: 35 Gy EBRT: 40 Gy in 20 fractions	2 Gy/fraction; 35 Gy over 48 hours	nd	2cm	nd	
Wallner 2005 16086912 USA	LDRBT (125 Gy) + EBRT (20 Gy)	83	67	nd	100%	7	2-6: 10.8% 7: 78.3% 8-10: 7.2%	23%	125 Gy LDRBT, 20 Gy EBRT	nd	nd	2 cm margin, 1.0 cm posteriorly	nd	B
	LDRBT (125 Gy) + EBRT (44 Gy)	76	67	nd	100%	6.7	2-6: 15.8% 7: 75% 8-10: 9.2%	41%	125 Gy LDRBT, 44 Gy EBRT	nd	nd	nd	nd	

Table D2. Characteristics of prospective cohort studies that compared combinations of radiotherapies with EBRT or LDRBT

Author Year [UI] Country	Intervention(s) or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobilization technique	Applied margins for PTV	Planning algorithm	Quality Comments
Lev 2009 18719947 US	EBRT (IMRT) + HDRBT	49	68.4	White 89.8, black 4.1, Hispanic 4.1, Asian 2.0	nd	nd	nd	nd	nd	nd	nd	nd	nd	B com-2 com-6
	EBRT (IMRT) + LDRBT	61	67.2	White 82, black 11.7, Hispanic 3.3, asian 3.3	nd	nd	nd	nd	nd	nd	nd	nd	nd	
Soumarova 2007 17455870 Czech Republic	EBRT (3D CRT)	57	69.9	nd	80.7	≤10: 47.4% 10-20: 28.1% >20: 24.5%	<4: 22.8% 4-6: 54.8% ≥7: 10.5% Unknown: 12.3%	36.8%	Different dosages in different phrases. See table 2.	nd	nd	?	nd	C com-2
	EBRT (3D CRT) + HDRBT	40	68.7	nd		≤10: 35% 10-20: 32.5% >20: 32.5%	<4: 25% 4-6: 65% ≥7: 10%	42.5%	3D CRT: 45Gy in 25 fractions if low risk; 50.4 Gy in 28 fractions if intermediate or high risk BT: 2 x 8 Gy (see table 1.)	nd	nd	0.3cm (average)	nd	

Table D3. Characteristics of retrospective cohort studies that compared combinations of radiotherapies with EBRT or LDRBT

Author Year [UI] Country	Intervention(s) or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobi-lization technique	Applied margins for PTV	Planning algorithm	Quality Comments
Abdel-Wahab M 2008 18374503 US	EBRT	48400	70.5(6.9)	nd	79.9%	nd	nd	nd	nd	nd	nd	nd	nd	B
	BT	10223	66.7(7.7)	nd	94.5%	nd	nd	nd	nd	nd	nd	nd	nd	
	EBRT + BT	9096	66.7(7.8)	nd	79.4%	nd	nd	nd	nd	nd	nd	nd	nd	
	No RT	40733	73.1(9.0)	nd	78.1%	nd	nd	nd	nd	nd	nd	nd	nd	
Elliot 2007 17570425 US	BT, BT+EBRT, EBRT, WW	6597	>60yr: 1655 (25%) 60-69 yr: 2607 (40%) 70 yr or older: 2334 (35%)	≤4: 952 (14%) 4.1-10: 4116 (62%) 10.1-20: 1029 (16%) >20: 499 (8%)	98%	≤4: 952 (14%) 4.1-10: 4116 (62%) 10.1-20: 1029 (16%) >20: 499 (8%)	2-6: 4304 (65%) 7: 1723 (26%) 8-10: 569 (9%)	nd	nd	nd	nd	nd	nd	B com-2
Joseph 2008 18627617 Canada	EBRT	88	69 (46-84)	nd	90%	8.7 median (1.7-161.8)	55 scored 2-6 21 scored 7 12 scored 8-10	nd	66-70	2	nd	1-2 cm	nd	B

Author Year [UI] Country	Intervention(s) or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobi-lization technique	Applied margins for PTV	Planning algorithm	Quality Comments
	EBRT+HDRBT	23	69 (50-78)	nd	83%	8.9 median (0.8-51.9)	14 scored 2-6 7 scored 7 2 scored 8-10	nd	16.5	3 fractions	nd	0.2-0.3 cm	nd	
Song 2008 18714275 US	EBRT (IMRT) + LDRBT	15	63.0(7.1)	nd	100%	7.4	6.9	nd	50.4 (95 for brachytherapy component)	1.8	Customized Thermoplastic mold	1 cm 0.6-cm posteriorly.	MSKCC in house treatment planning system, most plans consisted of 5 coplanar beams at 225 degrees, 285 degrees, 0 degrees, 75 degrees, and 135 degrees.	C com-2
	LDRBT	15	65.7(7.6)	nd	100%	6.0	6.1	nd	144	nd	nd	0.5 cm, 0 cm posteriorly	MSKCC in house brachytherapy planning system	

Author Year [UI] Country	Intervention(s) or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobi-lization technique	Applied margins for PTV	Planning algorithm	Quality Comments
Wong 2009 19670452 USA	EBRT (3D-CRT)	270	nd	nd	90	≤10: 71%, 10.1-20: 19%, ≥20: 10%	65% ≤6	161 (28%) patients who received 3D-CRT or IMRT Median ADT duration = 9 mo (range, 1-72 mo), depending on the risk category	45 Gy to the prostate and seminal vesicles, while the prostate was boosted to a median dose of 68.4 (range, 66-77 Gy)	1.8 to 2	nd	Customized blocking with a 1 - 2 cm margin from planning target volume to block edge	None	B
	EBRT (IMRT)	314	nd	nd	96	≤10: 76%, 10.1-20: 17%, ≥20: 7%	44% ≤6	161 (28%) patients who received 3D-CRT or IMRT Median ADT duration = 9 mo (range, 1-72 mo), depending on the risk category	Median dose of 75.6 (range, 75.6-77.4 Gy) to prostate gland; 50.4 Gy to seminal vesicles	nd	nd	0.6 - 1 cm	nd	

Author Year [UI] Country	Intervention(s) or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobi-lization technique	Applied margins for PTV	Planning algorithm	Quality Comments
	LDRBT	225	nd	nd	100	≤10: 86%, 10.1-20: 12%, ≥20: 2%	77% ≤6	72 (32%) received short-term ADT median duration = 3 mo (range, 2-14 mo)	Minimal peripheral dose was 144 Gy for I-125 and 120 Gy for pd-103	n/a	nd	n/a	nd	
	EBRT (3D-CRT)+LDRBT	44	nd	nd	98	≤10: 65%, 10.1-20: 30%, ≥20: 5%	45% ≤6	12 (27%) received short-term ADT. Duration was not reported.	45 gy of EBRT to the prostate and seminal vesicles using 3D-CRT, followed by a BRT boost of 110 Gy using I-125, or 90 Gy using Pd-103 seeds.	nd	nd	nd	nd	
Zelevsky 2008 18299108 US	LDRBT + EBRT (IMRT)	127	<65: 58 ≥65: 69	nd	98%	<10: 106 10-20: 20 >20: 1	<=6 – 53 7 – 68 >= - 6	34%	110 Gy (I-125 dose) + 50.4 Gy (IMRT)	1.8 Gy fractions (IMRT)	nd	1 cm around CTV(prostate and seminal vesicles) 0.3 cm margin posteriorly	Genetic optimization	C com-1 com-6
	LDRBT	216	<65: 88 ≥65: 128	nd	100%	<10: 207 10-20: 9 >20: 0	<=6 – 206 7 – 10 >= - 0	1%	145 Gy	nd	nd		nd	

com-1: No adjustment for potential confounders
com-2: incomplete reporting (e.g., little or no description of study eligibility criteria or methods, missing data)
com-3: historical comparison

com-4: incomplete statistical analysis (e.g., P value not reported)
com-5: different lengths of follow-up between groups
com-6: baseline participant characteristics not entirely comparable between groups (no adjustment)
com-7: loss to follow-up ≥20% (only for RCTs)
com-8: method of randomization not reported

Table D4. Genitourinary toxicity: combinations of radiotherapies vs. EBRT or LDRBT (qualitative)

Outcome	Interventions or comparisons (total sample size)	Findings		Quality
Prospective cohort studies				
Disease-specific QoL: urinary scores	HDRBT+EBRT (N=49) vs. LDRBT+EBRT (N=61)	Lev (2009)	Better	B
Acute GU ≥ Grade 3	HDRBT+EBRT (N=40) vs. EBRT (N=57)	Soumarova (2007)	No diff	C
Retrospective cohort studies				
Disease-specific QoL: urinary scores	LDRBT+EBRT (N=15) vs. LDRBT (N=15)	Song (2008)	Worse	C
Acute GU ≥ Grade 3	LDRBT+EBRT (N=44)* vs. EBRT (N=314)	Wong (2009)	No diff	B
	LDRBT+EBRT (N=44)* vs. LDRBT (N=215)	Wong (2009)	No diff	
	LDRBT+EBRT (N=127) vs. LDRBT (N=216)	Zelefsky (2008)	No diff	C
Late GU ≥ Grade 3	LDRBT+EBRT (N=44)* vs. EBRT (N=314)	Wong (2009)	**Worse**	B
	LDRBT+EBRT (N=44)* vs. LDRBT (N=215)	Wong (2009)	No diff	
	LDRBT+EBRT (N=127) vs. LDRBT (N=216)	Zelefsky (2008)	No diff	C
Urethral strictures	BT+EBRT (N=231) vs. EBRT (N=645)	Elliott (2007)	**Worse**	B

QoL, quality of life; diff, difference

Better: net difference in urinary scores improved >1 point or statistically significant risk difference in increasing acute/late GU toxicity or other adverse outcomes, comparing first treatment listed with second treatment listed

No diff: net difference in urinary scores within 1 point or no statistically significant risk difference in acute/late GU toxicity and other adverse outcomes, comparing first treatment listed with second treatment listed

Worse: net difference in urinary scores worsen >1 point or statistically significant risk difference in decreasing acute/late GU toxicity or other adverse outcomes, comparing first treatment listed with second treatment listed

Bold words signify statistical significance P<0.05

*The same LDRBT+EBRT group was compared to EBRT (IMRT) or LDRBT group

Table D5. Gastrointestinal toxicity: combinations of radiotherapies vs. EBRT or LDRBT (qualitative)

Outcome	Interventions or comparisons (total sample size)	Findings		Quality
Prospective cohort studies				
Disease-specific QoL: bowel scores	HDRBT+EBRT (N=49) vs. LDRBT+EBRT (N=61)	Lev (2009)	No diff	B
Acute GI ≥ Grade 3	HDRBT+EBRT (N=40) vs. EBRT (N=57)	Soumarova (2007)	Better	C
Retrospective cohort studies				
Acute GI ≥ Grade 3	LDRBT+EBRT (N=44)* vs. EBRT (N=314)	Wong (2009)	No diff	B
	LDRBT+EBRT (N=44)* vs. LDRBT (N=215)	Wong (2009)	No diff	
	LDRBT+EBRT (N=127) vs. LDRBT (N=216)	Zelefsky (2008)	No diff	C
Late GI ≥ Grade 3	LDRBT+EBRT (N=44)* vs. EBRT (N=314)	Wong (2009)	No diff	B
	LDRBT+EBRT (N=44)* vs. LDRBT (N=215)	Wong (2009)	No diff	
	LDRBT+EBRT (N=127) vs. LDRBT (N=216)	Zelefsky (2008)	No diff	C

QoL, quality of life; diff, difference

Better: net difference in urinary scores improved >1 point or statistically significant risk difference in increasing acute/late GU toxicity or other adverse outcomes, comparing first treatment listed with second treatment listed

No diff: net difference in urinary scores within 1 point or no statistically significant risk difference in acute/late GU toxicity and other adverse outcomes, comparing first treatment listed with second treatment listed

Worse: net difference in urinary scores worsen >1 point or statistically significant risk difference in decreasing acute/late GU toxicity or other adverse outcomes, comparing first treatment listed with second treatment listed

Bold words signify statistical significance P<0.05

*The same LDRBT+EBRT group was compared to EBRT (IMRT) or LDRBT group

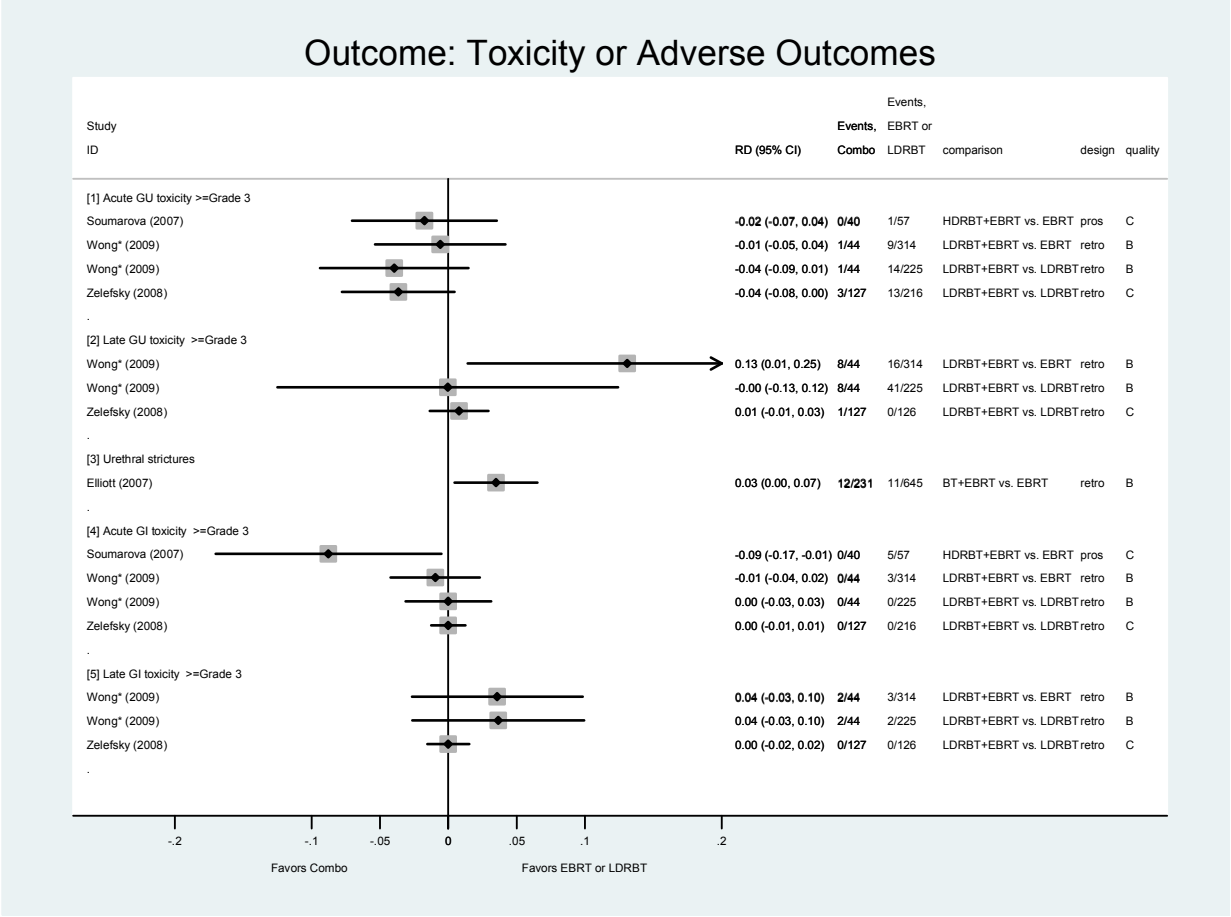
Table D6. Urinary and bowel dysfunction scores: combination of radiation therapies vs. EBRT or LDRBT

Author Year [UI] Country	Outcome	Intervention	Follow -up, yr	No. Analyzed	Baseline	Change (SD)	Net diff	95%CI	P btw	Quality
Song 2008 18714275 US	4 month IPSS	EBRT (IMRT) + LDRBT	0.33	15	nd	12.0 (8.0)[A]	2.5	nd	0.39	C
		LDRBT	0.33	15	nd	9.5 (7.0) [A]				
Lev 2009 18719947 US	PSSR Urinary Score	EBRT (IMRT) + HDRBT	1	49	26.70	2.79 (19.34)	-6.19	-13.6, 1.25	0.10	B
		EBRT (IMRT) + LDRBT	1	61	17.00	8.98 (19.7)				
	PSSR Bowel Score	EBRT (IMRT) + HDRBT	1	49	10.22	5.25(14.36)	0.52	-4.92, 5.96	0.85	
		EBRT (IMRT) + LDRBT	1	61	7.6	4.73 (14.3)				

nd, no data or not done; IPSS, International Prostate Symptom Score (range, in which higher scores indicate increased dysfunction); PSSR, Prostate Symptom Self Report (range from 0-100, in which higher scores indicate greater symptom unpleasantness)

[A] Value is IPSS score at four months

Figure D1. Genitourinary and gastrointestinal toxicity: combination of radiation therapies vs. EBRT or LDRBT



*Wong (2009) compared LDRBT+EBRT to either EBRT or LDRBT

Appendix E. Detailed results for intra-SBRT and intra-EBRT comparisons

Intra-SBRT comparisons

No RCTs or prospective cohort studies compared different SBRT doses or techniques. One retrospective study with a median follow-up of 30 months compared the use of 35 Gy in 5 fractions of 7 Gy (N = 50; first 50 patients) versus 36.25 Gy in 5 fractions of 7.25 Gy (N = 254) to treat patients with clinically localized prostate cancer (all T1 or T2).[31] Acute RTOG grade 2 bladder and rectal toxicities were comparable in the two groups (bladder 4% vs. 4.7%; rectal 4% vs. 3.6%, respectively). Late RTOG grade 3 bladder and rectal toxicities were also comparable (bladder 0% vs. 0.5%; rectal 0% vs. 0%). In those patients who did not receive ADT and had a minimum follow-up of 12 months, no biochemical failure occurred in the 35 Gy group (denominator not reported); four biochemical failures occurred in the 36.25 Gy group (denominator not reported). This study was rated C because of historical comparison and incomplete analysis and reporting.

Intra-EBRT Comparisons

Eight RCTs, 3 prospective cohorts, and 13 retrospective cohorts reported intra-EBRT comparisons based on different radiation dosages, fractions or modalities. We grouped these studies based on these comparisons.

EBRT Dose Comparisons (Tables E1-E3; Figures E1-E3)

Randomized controlled trials (RCTs) (Table E1)

Three RCTs reported in 5 publications compared conventional dose EBRT with high dose EBRT.[32-36] The sample size in these studies ranged from 301 to 664. One study included only patients with T1 or T2 disease,[35] while the other two studies included some patients with T3 or higher stage disease. Two studies did not include patients who received ADTs,[32, 33, 35] while the third trial included about 20% of patients who also received some form of ADTs. Of note, one trial used a proton therapy boost after initial photo therapy treatment.[35] The methodological quality of all 3 RCTs were rated B. A common reason for downgrading the quality ratings in these studies was suboptimal reporting (e.g., unclear descriptions on the conduct of a trial or discrepancies in reporting of results).

Freedom from biochemical failure (Figure E1)

Two RCTs reported that the freedom from biochemical or clinical failure at 5 years was significantly increased for patients treated with higher dose compared to those treated with lower dose (91% vs. 79%; P <0.001[35] and 85% vs. 78%; P = 0.004.[32, 33]) The other trial reported a non-significant difference between the 2 groups in a subset analysis of low/intermediate risk patients (low dose 73.3% vs. high dose 81.4%).[34]

Genitourinary toxicity (Table E2)

One RCT provided data on genitourinary toxicity.[35] Comparing high with low dose, the incidence rates of acute genitourinary toxicity grade 3 or greater were 1.5% versus 1% (P = NS) and the rates for late genitourinary toxicity were 0.5% versus 1.5%, respectively.

Gastrointestinal toxicity (Table E3)

The same RCT also provided data on gastrointestinal toxicity. Comparing high with low dose, the incidence rates of acute gastrointestinal toxicity grade 3 or greater were 0% versus 1% (P = NS) and the rates for late gastrointestinal toxicity were 0.5% versus 0.5%, respectively.

Prospective studies (Table E1)

Two prospective cohorts reported dose comparisons with sample sizes ranged from 402 to 956. [41, 68] One study enrolled only patients with T1 or T2 disease and both of them had up to 40% of the patients receiving some form of ADTs. First study divided patients into three groups based on clinical stage.[41] Group 1 patients had clinical Stage T1 disease with minimal risk of seminal vesicle invasion. Group 2 patients had a risk of seminal vesicle invasion more than 15%. Group 3 patients had clinical Stage T3 disease. Each group was then divided into five levels and treated with different radiation doses. This review excluded group 3 because this group included patients with stage T3 disease. The incidence rates of late grade 3 or greater genitourinary toxicity were 1%, 4%, 5%, 3%, and 5% for group 1 and 3%, 2%, 3%, 6%, and 6% for group 2 at dose levels of I through V. The incidence rates for late grade 3 or greater gastrointestinal toxicity were 1%, 0%, 1%, 3%, and 4% for group 1 and 3%, 0%, 3%, 2%, and 7% for group 2 at dose levels of I through V. No further statistical analysis was provided because these rates were not large enough to be modeled. The methodological quality of this study was rated B.

Second study only provided analysis on late grade 2 or greater genitourinary toxicity, no separate analysis for late grade 3 or greater was provided. There was no significant difference between the two arms in late grade 2 or greater genitourinary toxicity (21% in 74 Gy arm vs. 17.3% in 70 Gy arm; P = 0.26).[68] Similarly, the late grade 2 or greater gastrointestinal toxicity was also not significantly different between the two arms (9.2% in 74 Gy arm vs. 6.1% in 70 Gy arm; P = 0.31). The methodological quality of this study was rated C because there was no adjustment for potential confounders.

Retrospective studies (Table E1)

Nine retrospective cohorts in 10 publications reported dose comparisons with sample size ranged from 80 to 2,047.[22, 37-40, 42, 69-72] All studies included patients with T3 or higher stage disease (5% to 20%) and only two studies did not include patients who received some form of ADTs.[37, 39] In terms of the methodological quality, 6 studies were rated B and 3 were rated C. A common reason for downgrading these studies was suboptimal reporting.

Freedom from biochemical failure (Figures E1-E2)

Five cohorts in six publications comparing different radiation doses reported freedom from biochemical failure at intervals ranging from 5 to 10 years.[22, 37-40, 72] All of the studies consistently reported that higher radiation dose administered were associated with increased rates of freedom from biochemical failure.

Genitourinary toxicity (Table E2)

Two studies reported acute genitourinary toxicity.[22, 71, 72] The incidence rates of acute genitourinary toxicity grade 3 or greater were not significantly different between the arms in both studies. Four studies reported late genitourinary toxicity and the incidence rates of late genitourinary toxicity grade 3 or greater were also not significantly different between the arms in any of the studies.[22, 38, 69, 71, 72]

Gastrointestinal toxicity (Table E3)

Two studies reported the incidence rates of acute gastrointestinal toxicity grade 3 or greater were not significantly different between the arms in both studies.[22, 71, 72] Five studies reported the incidence rates of late gastrointestinal toxicity grade 3 or greater were not significantly different between the arms in any of the studies.[22, 38, 42, 69, 71, 72]

Table E1. Characteristics of studies that compared different EBRT doses

Author Year [UI] Country	Intervention(s) or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobilization technique	Applied margins for PTV	Planning algorithm	Comments
RCT														
Peeters 2006 16648499 Netherlands	EBRT (68 Gy)	331	68.6	nd	63	≤4: 8 4-10: 29 10-20: 38 20-60: 26	2-4: 32 5-7: 51 8-10: 17	22	68	2	nd	1.0cm	nd	B com-8
	EBRT (78 Gy)	333	68.8	nd	63	≤4: 6 4-10: 36 10-20: 38 20-60: 21	2-4: 28 5-7: 59 8-10: 14	21	78	2	nd	1.0cm during the first 68 Gy, 0.5cm for the last 10 Gy	nd	
Pollack 2002 2128107 and Kuban 2008 17765406 USA	EBRT (3D-CRT (70 Gy) arm)	150	nd	nd	83	<10: 65 >10: 35	2-6: 46 7: 37 8-10: 17	0	70	nd	nd	1.25–1.5 cm anterior & inferior 0.75–1.0 cm posterior & superior	nd	B com-8
	EBRT (3D-CRT (78 Gy) arm)	151	nd	nd	77	<10: 65 >10: 35	2-6: 50 7: 32 8-10: 18	0	78	nd	nd	1.25–1.5 cm anterior & inferior 0.75–1.0 cm posterior & superior	nd	
Zietman 2005 16160131 and Zietman 2010 20124169 USA	EBRT (Conventional 70.2 GyE)	197	67	White: 89.3 Black: 6.1 Hispanic: 2	100	<4: 12 4-<10: 74 10-15: 14	2-6: 75 7: 15 8-10: 9	0	70.2 GyE	1.8 GyE	casts of thermal plastic or body foam with rectal balloon	0.7 – 1.0 cm	nd	B com-2

Author Year [UI] Country	Intervention(s) or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobilization technique	Applied margins for PTV	Planning algorithm	Comments
	EBRT (High 79.2 GyE)	195	66	White: 91.3 Black: 2.6 Hispanic: 3.6	100	<4: 11 4-<10: 74 10-15: 15	2-6 : 75 7: 15 8-10: 8	0	79.2 GyE	1.8 GyE	casts of thermal plastic or body foam with rectal balloon	0.7 – 1.0 cm	nd	
Prospective Cohort Study														
Lin 2007 17958696 Australia	EBRT (70Gy 3D CRT)	292	69 (overall)	nd	90	<10: 43.8 10-20: 36.8 >20: 19.4	≤6: 44 7: 39.1 8-10: 16.9	57.8	74	2	nd	1.0-1.5cm (1.0 cm posteriorly) added for PTV1, 0.5-1.0cm (<0.5cm posteriorly) added for PTV 2	nd	C com-2
	EBRT (74Gy 3D CRT)	110							70	2	nd		nd	
Michalski 2010 19577865 USA	EBRT (3D-CRT) Level 1, Disease group 1	75		nd	100	≤10: 75 20: 24 ≥20: 1	2-6: 93 7: 7 8-10: 0	8	68.4	1.8	nd	0.5-1.0 cm	nd	B com-2
	EBRT (3D-CRT) Level 1, Disease group 2	33		nd	100	≤10: 42 20: 33 ≥20: 24	2-6: 36 7: 36 8-10: 27	15	68.4	1.8	nd	0.5-1.0 cm	nd	
	EBRT (3D-CRT) Level 2, Disease group 1	97		nd	100	≤10: 81 20: 19 ≥20: 0	2-6: 95 7: 5 8-10: 0	20	73.8	1.8	nd	0.5-1.0 cm	nd	
	EBRT (3D-CRT) Level 2, Disease group 2	108		nd	100	≤10: 43 20: 35 ≥20: 22	2-6: 41 7: 41 8-10: 19	48	73.8	1.8	nd	0.5-1.0 cm	nd	
	EBRT (3D-CRT) Level 3, Disease group 1	104		nd	100	≤10: 87 20: 13 ≥20: 1	2-6: 94 7: 6 8-10: 0	30	79.2	1.8	nd	0.5-1.0 cm	nd	

Author Year [UI] Country	Intervention(s) or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobilization technique	Applied margins for PTV	Planning algorithm	Comments
	EBRT (3D-CRT) Level 3, Disease group 2	63		nd	100	≤10: 43 20: 38 ≥20: 19	2-6: 22 7: 46 8-10: 32	68	79.2	1.8	nd	0.5-1.0 cm	nd	
	EBRT (3D-CRT) Level 4, Disease group 1	115		nd	100	≤10: 86 20: 14 ≥20: 0	2-6: 91 7: 9 8-10: 0	22	74	2	nd	0.5-1.0 cm	nd	
	EBRT (3D-CRT) Level 4, Disease group 2	141		nd	100	≤10: 50 20: 32 ≥20: 18	2-6: 21 7: 56 8-10: 23	52	74	2	nd	0.5-1.0 cm	nd	
	EBRT (3D-CRT) Level 5, Disease group 1	119		nd	100	≤10: 77 20: 23 ≥20: 0	2-6: 87 7: 13 8-10: 0	8	78	2	nd	0.5-1.0 cm	nd	
	EBRT (3D-CRT) Level 5, Disease group 2	101		nd	100	≤10: 43 20: 41 ≥20: 17	2-6: 12 7: 71 8-10: 17	34	78	2	nd	0.5-1.0 cm	nd	
Retrospective Cohort Study														
Eade 2007 17398026 USA	EBRT (3D-CRT: <70 Gy)	43	73	nd	100	<10: 58 10-20: 28 >20: 14	2-6: 98 7: 2 8-10: 0	0	70	nd	alpha cradle cast	1.0 cm	nd	B com-5
	EBRT (3D-CRT: 70-74.9 Gy)	552	69		95	<10: 66 10-20: 23 >20: 11	2-6: 80 7: 18 8-10: 2	0	70-74.9	nd			nd	
	EBRT (3D-CRT: 75-79.9 Gy)	568	68		96	<10: 62 10-20: 27 >20: 11	2-6: 81 7: 15 8-10: 4	0	75-79.9	nd			nd	
	EBRT (3D-CRT: ≥80 Gy)	367	69		96	<10: 58 10-20: 34 >20: 8	2-6: 45 7: 51 8-10: 4	0	≥80	nd			nd	

Author Year [UI] Country	Intervention(s) or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobilization technique	Applied margins for PTV	Planning algorithm	Comments
Goldner 2009 19240995 Austria	EBRT 66 Gy (1994-1998)	117	70	nd	85	≤10: 48 >10-20: 39	≤6: 93	44	66	nd	Endorectal balloon	1.5-2.0 cm	nd	B com-3
	EBRT 70 Gy (1998-2003, not high risk)	165	71		96	≤10: 69 >10-20: 30	≤6: 80	68	70		nd	0.5-1.0 cm	nd	
	EBRT 74 Gy (1998-2003, high risk only; 2003+, all pts)	116	71		74	≤10: 44 >10-20: 31	≤6: 62	81	74		nd	0.5-1.0 cm	nd	
Hanssen 2008 19031926 Norway	EBRT (Conformal technique)	57	65.5	nd	nd	nd	nd	nd	70	2	nd	nd	nd	C com-1
	EBRT (BeamCath® technique)	23	66.2	nd	nd	nd	nd	nd	76	2	nd	1.0-1.5 cm	nd	
Jani AB 2007 17241095 USA	EBRT (4,6 field or 3D conformal)	373	67.6	White: 51% African American: 43% Other: 6%	82	9.5	2-6: 62 7: 28 8-10: 9 Not recorded:1	53	70.0	1.8-20	nd	1.0 cm	AcQSim VoxelQ software	C com-2
	EBRT (IMRT)	108	69	White: 42% African American: 54% Other: 4%	99	7.6	2-6: 48 7: 45 8-10: 7	51	76.0		nd	1.0 cm & 0.5 cm posteriorly	Corvus inverse planning system	
Jani AB 2007 16983394 USA	EBRT (4,6 field or 3D conformal)	355	67.7	White: 50% African American: 43% Other: 6%	82	9.5	2-6: 63 7: 28 8-10: 9	38	70.0	1.8-20	nd	1.0 cm	AcQSim VoxelQ software	C com-2

Author Year [UI] Country	Intervention(s) or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobilization technique	Applied margins for PTV	Planning algorithm	Comments
	EBRT (IMRT)	106	68.9	White: 42% African American: 55% Other: 4%	98	7.6	2-6: 49 7: 44 8-10: 7	51	76.0		nd	1.0 cm & 0.5 cm posteriorly	Corvus inverse planning system	
Kupelian 2008 17996382 USA	EBRT (<72 Gy)	552	69 (overall for all 3 groups)	Black: 23 (overall)	93	>4 to ≤10: 42 >10 to ≤20: 27 >20: 22	2-6: 63	0	68.4	1.8-2.0	nd	nd	nd	B com-6
	EBRT (72-82 Gy)	215			93	>4 to ≤10: 63 >10 to ≤20: 23 >20: 7	2-6; 69	0	78		nd	nd	nd	
	EBRT (≥82 Gy)	152			100	>4 to ≤10: 74 >10 to ≤20: 17 >20: 1	2-6 80	0	70 (equiv 83 Gy)	2.5	nd	nd	nd	
Wong 2009 19670452 And Vora 2007 17398023 USA	EBRT (3D-CRT)	270	nd	nd	90	≤10: 71 10.1-20: 19 ≥20: 10	≤6: 65	17	68.4	1.8 to 2	nd	1.0-2.0 cm	none	B
	EBRT (IMRT)	314	nd	nd	96	≤10: 76 10.1-20: 17 ≥20: 7	≤6: 44	36	75.6	nd	nd	0.6-1.0 cm	nd	
	BT	225	nd	nd	100	≤10: 86 10.1-20: 12 ≥20: 2	≤6: 77	32	I-125: 144 Gy pd-103: 120 Gy	n/a	nd	n/a	nd	

Author Year [UI] Country	Intervention(s) or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobilization technique	Applied margins for PTV	Planning algorithm	Comments
	EBRT+BT	44	nd	nd	98	≤10: 65 10.1-20: 30 ≥20: 5	≤6: 45	27	EBRT: 45 Gy, followed by 110 Gy using I-125, or 90 Gy using Pd-103 seeds.	nd	nd	nd	nd	
Zelefsky 2008 18280056 USA	EBRT (3-D CRT)	2047	69 (overall)	nd	83	<10: 56 10-20: 26 >20: 18	≤6: 47 7: 36 ≥8: 17	52	64.8-75.6	1.8	nd	1.0 cm & 0.6 cm posteriorly	nd	B com-3
	EBRT (IMRT)								81 or 86.4	1.8	nd	1.0 cm & 0.6 cm posteriorly	nd	
Zelefsky 2008 18313526 USA	EBRT (3-D CRT-70.2Gy)	358	69 (overall)	nd	nd	nd	nd	43 (overall)	70.2	1.8	nd	nd	nd	B com-2
	EBRT (3-D CRT-75.6Gy)	472			nd	nd	nd		75.6	1.8	nd	nd	nd	
	EBRT (IMRT-81Gy)	741			nd	nd	nd		81	nd	nd	nd	nd	

com-1: No adjustment for potential confounders
com-2: incomplete reporting (e.g., little or no description of study eligibility criteria or methods, missing data)
com-3: historical comparison
com-4: incomplete statistical analysis (e.g., P value not reported)
com-5: different lengths of follow-up between groups
com-6: baseline participant characteristics not entirely comparable between groups (no adjustment)
com-7: loss to follow-up ≥20% (only for RCTs)
com-8: method of randomization not reported

Table E2. Genitourinary toxicity: EBRT dose comparisons (qualitative)

Outcome	Interventions or comparisons (total sample size)	Study	Findings	Quality
RCTs				
Acute GU ≥ Grade 3	Higher dose (N= 195) vs. lower dose (N= 196)	Zietman (2005)	No diff	B
Late GU ≥ Grade 3	Higher dose (N= 195) vs. lower dose (N= 196)	Zietman (2005)	No diff	B
Prospective cohort studies				
Late GU ≥ Grade 3	Higher dose (N= 958) vs. lower dose (N= 400)	Michalski (2010)	No diff	B
		Lin (2007)	No diff	C
Retrospective cohort studies				
Acute GU ≥ Grade 3	Higher dose (N= 422) vs. lower dose (N= 643)	Wong (2009)	No diff	B
		Jani (2007)	No diff	C
	Higher (N=741[B]) vs. lower dose (N=830 [B])	Zelefsky (2008)[A]	**High is worse**	B
Late GU ≥ Grade 3	Higher dose (N= 724) vs. lower dose (N= 799)	Goldner (2009)	No diff	B
		Wong (2009)	No diff	B
		Hanseen (2008)	No diff	C
		Jani (2007)	No diff	C
	High (N=741), medium (N=472), low (N=358)	Zelefsky (2008)[A]	**High is worse**	B

Better: statistically significant risk difference in increasing acute/late GI toxicity or other adverse outcomes, comparing EBRT higher dose with EBRT lower dose
No difference: no statistically significant risk difference in acute/late GI toxicity and other adverse outcomes, comparing EBRT higher dose with EBRT lower dose
Worse: statistically significant risk difference in decreasing acute/late GI toxicity or other adverse outcomes, comparing EBRT higher dose with EBRT lower dose
Bold words signify statistical significance P<0.05

[A] ≥ Grade 2 GU toxicity
[B] estimated; as high (81 Gy) was only worse for those with IMRT, unclear how many without IMRT received high dose

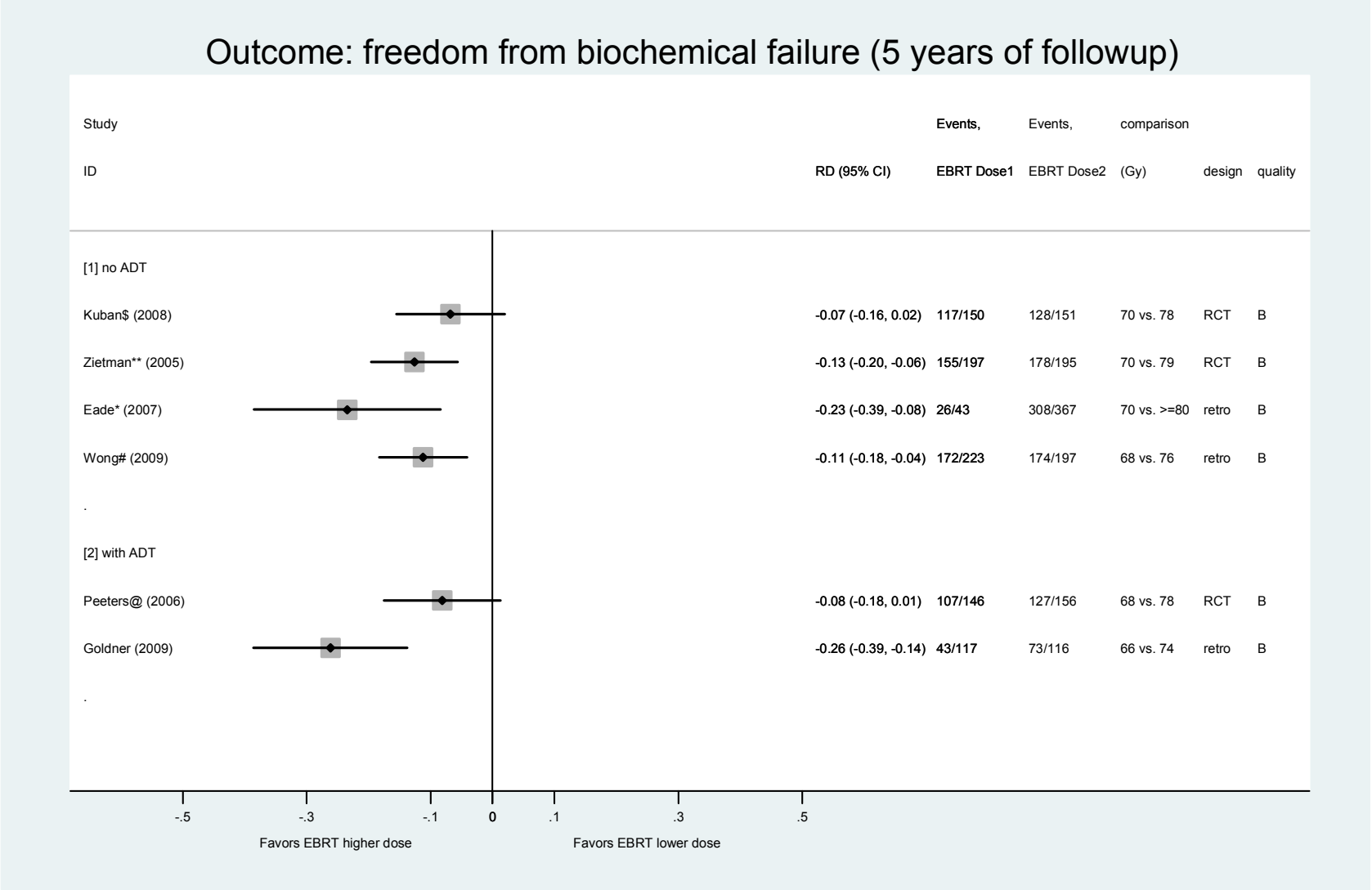
Table E3. Gastrointestinal toxicity: EBRT dose comparisons (qualitative)

Outcome	Interventions or comparisons (total sample size)	Study	Findings	Quality
RCTs				
Acute GI ≥ Grade 3	Higher dose (N= 195) vs. lower dose (N= 196)	Zietman (2005)	No diff	B
Late GI ≥ Grade 3	Higher dose (N= 195) vs. lower dose (N= 196)	Zietman (2005)	No diff	B
Prospective cohort studies				
Late GI ≥ Grade 3	Higher dose (N= 958) vs. lower dose (N= 400)	Michalski (2010)	No diff	B
		Lin (2007)	No diff	C
Retrospective cohort studies				
Acute GI ≥ Grade 3	Higher dose (N= 422) vs. lower dose (N= 643)	Wong (2009)	No diff	B
		Jani (2007)	No diff	C
	High (N=741), medium (N=472), low (N=358)	Zelefsky (2008)[A]	No diff[a]	
Late GI ≥ Grade 3	Higher dose (N= 724) vs. lower dose (N= 799)	Goldner (2009)	No diff	B
		Wong (2009)	No diff	B
		Hanseen (2008)	No diff	C
		Jani (2007)	No diff	C
	High (N=741), medium (N=472), low (N=358)	Zelefsky (2008)[A]	**medium is worst**	B

Better: statistically significant risk difference in increasing acute/late GI toxicity or other adverse outcomes, comparing EBRT higher dose with EBRT lower dose
No difference: no statistically significant risk difference in acute/late GI toxicity and other adverse outcomes, comparing EBRT higher dose with EBRT lower dose
Worse: statistically significant risk difference in decreasing acute/late GI toxicity or other adverse outcomes, comparing EBRT higher dose with EBRT lower dose
Bold words signify statistical significance P<0.05

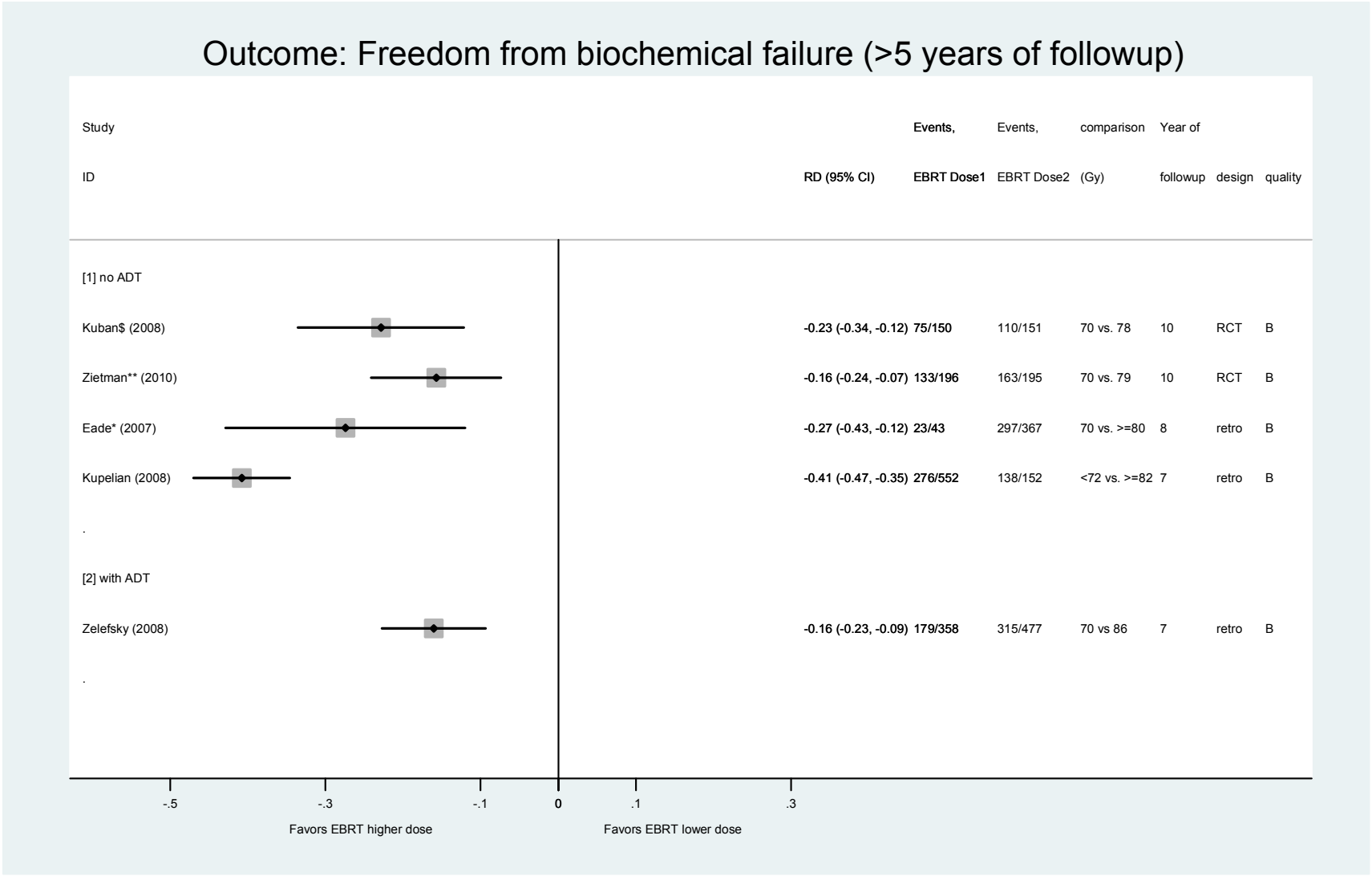
[a] ≥ Grade 2 GI toxicity

Figure E1. Freedom from biochemical failure: EBRT dose comparisons (5 years of follow-up)



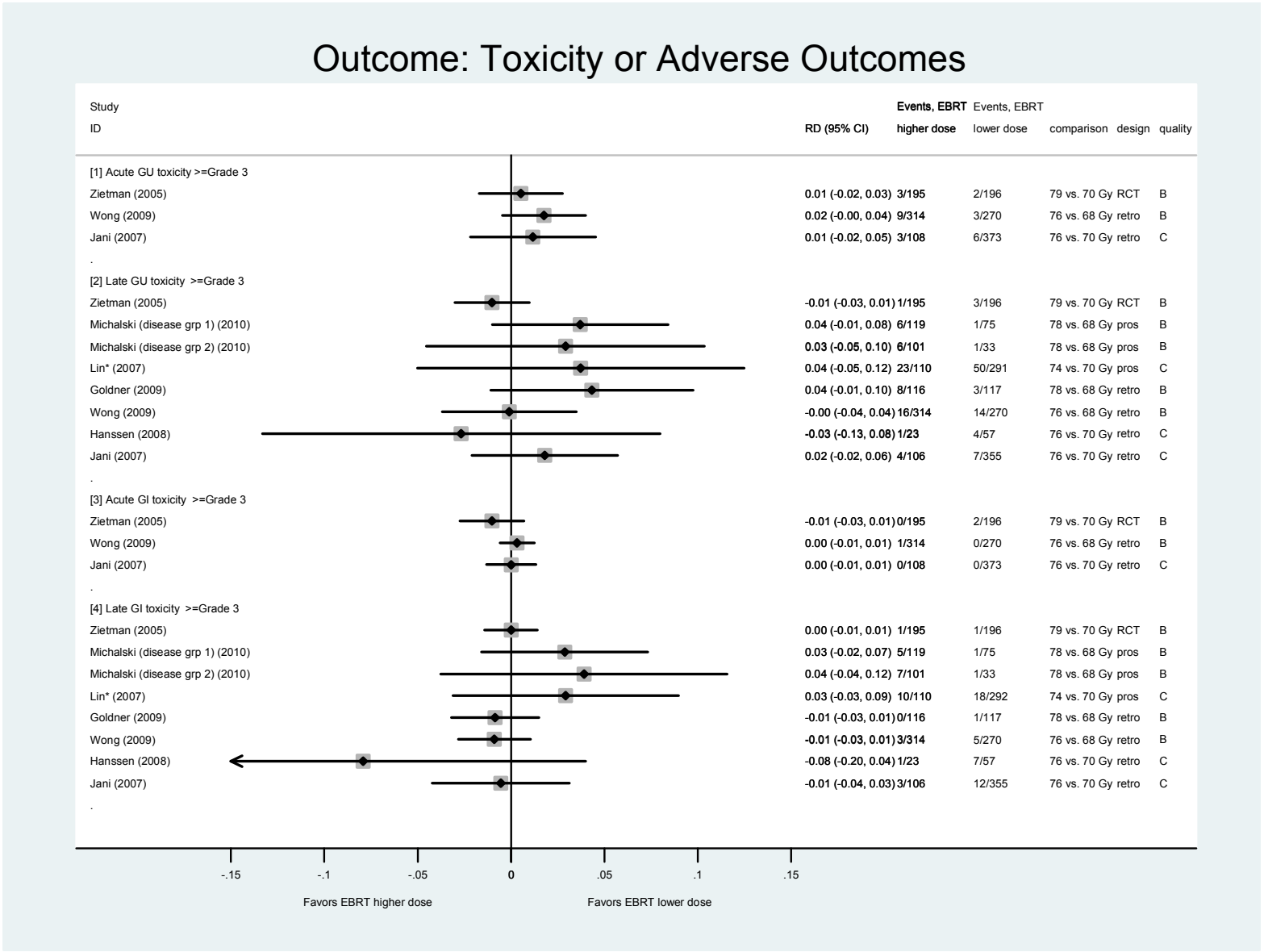
$Kuban (2008) also provided 10-year follow-up data; *Eade (2007) also provided 8-year follow-up data; #Data presented here were from a subgroup of patients who did no received ADT; @ Data presented here were from low and intermediate risk groups; **Zietman recently published 10-year follow-up data for patients originally reported in Zietman 2005 (see Figure 6)

Figure E2. Freedom from biochemical failure: EBRT dose comparisons (>5 years of follow-up)



$Kuban (2008) also provided 5-year follow-up data; *Eade (2007) also provided 5-year follow-up data; **Zietman 2010 provided follow-up data for patients originally reported in Zietman 2005

Figure E3. Genitourinary and gastrointestinal toxicity: EBRT dose comparisons



Standard vs. Hypofractionation EBRT Comparisons (Tables E4-E6; Figure E4)

Randomized controlled trials (RCTs) (Table E4)

Four RCTs compared standard fractionation with hypofractionation.[43, 44, 46, 73] The sample size ranged from 91 to 936. Two studies included only patients with T1 or T2 disease, [43, 44] two studies included up to 14% of patients with T3 or higher stage disease.[46, 73] One study included 44% of patients who received some form of ADTs.[46] The methodological quality of 3 studies were rated B and one was rated C. A common methodological deficiency in these studies was suboptimal reporting.

Biochemical control and survival

Three RCTs reported outcomes on biochemical control using a composite definition including clinical failure and PSA concentration.[43, 44, 73] One trial found a significant decrease in the probability of biochemical or clinical progression at 5 years in the standard fractionation compared to the hypofractionation arm (53% vs. 60%, yielding a risk difference of -7% (95% CI -12.6% to -1.4%)).[43] Overall survival at 5 years was estimated as 85% and 88% in the standard fractionation and the hypofractionation arms, respectively (HR 0.85; 95%CI, 0.63 to 1.15). One trial did not find a significant difference in the actuarial 5-year biochemical relapse free (with or without clinical relapse) survival between conventional EBRT (55.5%) and hypofractionated EBRT (57.4%).[44] One trial reported three cases of biochemical relapse (out of 43) in the standard arm and two cases in the hypofractionation arm (out of 46) during a 12-month follow-up. [73] No statistical comparison was provided.

Genitourinary toxicity (Table E5, Figure E4)

Two RCTs provided data on grade 3 or grade 4 genitourinary toxicity.[43, 46] One trial reported that the acute genitourinary toxicity was slightly lower in the standard fractionation arm (4.9%) compared with the hypofractionation arm (8.6%) (% difference -3.7%; 95% CI, -7.0% to -0.5%); however, late toxicity was similarly low in both arms (1.9%).[43] One trial reported that no patients in either arm experienced grade 3 or grade 4 genitourinary toxicity.[46]

Gastrointestinal toxicity (Table E6, Figure E4)

The same RCTs provided data on grade 3 or grade 4 gastrointestinal toxicity. One trial reported that the acute gastrointestinal toxicity was non-significantly lower in the standard fractionation arm (2.6%) compared with the hypofractionation arm (4.1%) (%difference -1.5%; 95% CI, -4.0% to 0.8%); however, late toxicity was similarly low in both arms (1.3%).[43] One trial reported that no patients in either arm experienced grade 3 or grade 4 gastrointestinal toxicity.[46]

Prospective studies

No prospective cohorts that compared standard fractionation with hypofractionation met our inclusion criteria.

Retrospective studies (Table E4-E6, Figure E4)

Two retrospective analyses of the same cohort (one using the accrued sample between 2002 and 2004[74] and the other using the accrued sample between 2002 and 2006[45]) reported the acute and late genitourinary or gastrointestinal toxicities. The first analysis had 130 patients and

reported the acute genitourinary and gastrointestinal toxicity among 3 different fractionation groups.[74] The acute genitourinary toxicity grade ≥3 was 2.7% in 2 Gy/fraction group, 0% in 3 Gy/fraction group, and 5.9% in 3.15Gy/fraction group. The acute gastrointestinal toxicity grade ≥3 were reported to be 2.7% in 2 Gy/fraction group, 0% in both 3Gy/fraction and 3.15Gy/fraction groups. The methodological quality of this analysis was rated C because there was no statistical adjustment for potential confounders.

The second analysis had 219 patients.[45] This study reported the late genitourinary or gastrointestinal toxicities. Comparing standard fractionation (2 Gy/fraction) with hypofractionation (either 3 Gy/fraction or 3.15 Gy/fraction), late genitourinary toxicity grade ≥3 was 0.8% versus 2.2% (P = NS); for late gastrointestinal toxicity grade ≥3, it was 1.5% versus 1.1% (P = NS). There was no statistical difference in the late toxicities between the 3 Gy/fraction and the 3.15 Gy/fraction groups (data not provided in the analysis). The methodological quality of this analysis was rated B.

Table E4. Characteristics of studies that compared different EBRT fraction sizes

Author Year [UI] Country	Intervention(s) or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobilization technique	Applied margins for PTV	Planning algorithm	Comments
RCT														
Lukka 2005 16135479 Canada	EBRT (Long arm: 66 Gy in 33 fractions)	470	70.3	nd	100	10.4(0.4-40)	2-6: 597: 338-10: 8	0	66	2	nd	1.5-cm & 1.0 cm posteriorly	nd	B com-8
	EBRT (Short arm: 52.5 Gy in 20 fractions)	466	70.0	nd	100	10.6(0.3-39)	2-6: 607: 298-10: 11	0	52.5	2.6	nd	1.5 cm & 1.0 cm posteriorly	nd	
Norkus 2009 19605967 Lithuania	EBRT (Standard fractionation)	44	65	nd	95	≤10: 100	≤6: 100	0	74	2	nd	0.8-1.0 cm	nd	C com-4, 8
	EBRT (Hypo fractionation)	47	63		98	≤10: 100	≤6: 96	0	57	13 fractions of 3 Gy; 4 fractions of 4.5 Gy	nd	0.8-1.0 cm	nd	
Pollack 2006 16242256 USA	Conventional fractionation IMRT	50	nd	nd	86	<10: 60 10-20: 30 >20: 10	5-6: 307: 488-10: 22	44	76	2	nd	0.8 cm & 0.5 cm posteriorly	Corvus treatment planning system	B com-2
	Hypofractionation IMRT	50	nd	nd	86	<10: 52 10-20: 32 >20: 16	5-6: 487: 368-10: 16	44	70.2	2.7	nd	0.7 cm & 0.3 cm posteriorly		

Author Year [UI] Country	Intervention(s) or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobilization technique	Applied margins for PTV	Planning algorithm	Comments
Yeoh 2006 16965866 Australia	EBRT (Conventional 2D or 3D RT-64 Gy)	109	69 overall	nd	100	<10: 49.5 10-20: 41 >20: 9	2-6: 81 7: 15 8-10: 4	0	64	2	nd	1.5 cm 95% isodose margin	Pinnacle	B com-7
	EBRT (Hypofractionated 2D or 3D RT-55 Gy)	108		nd	100	<10: 43.5 10-20: 38 >20: 18.5	2-6: 79 7: 14 8-10: 9	0	55	2.75	nd	1.5 cm 95% isodose margin	Pinnacle	
Retrospective Cohort Study														
Leborgne F 2008 18375075 Uruguay	EBRT (Standard fractionation)	74	68	nd	95 (overall)			36	78	2		1.1 cm & 0.5 cm posteriorly	XiO computerized treatment planning system	C com-1
	EBRT (Hypofractionation -3Gy/fraction)	22	70	nd				19	60	3		No PTV2 rectal shielding		
	EBRT (Hypofractionation -3.15Gy/fraction)	34	69	nd				29	63	3.15		No PTV2 rectal shielding		
Leborgne F 2009 19395194 Uruguay	EBRT (Standard fractionation)	130	68	nd	100	Median 8ng/ml	Median 6	31	63	3.15		1.1 cm & 0.5 cm posteriorly	XiO computerized treatment planning system	B
	EBRT (Hypo fractionation)	89	70		97	Median 10ng/ml	Median 6	35	78	2		No PTV2 rectal shielding		

com-1: No adjustment for potential confounders
com-2: incomplete reporting (e.g., little or no description of study eligibility criteria or methods, missing data)
com-3: historical comparison
com-4: incomplete statistical analysis (e.g., P value not reported)
com-5: different lengths of follow-up between groups
com-6: baseline participant characteristics not entirely comparable between groups (no adjustment)

com-7: loss to follow-up ≥20% (only for RCTs)
com-8: method of randomization not reported

Table E5. Genitourinary toxicity: EBRT fraction size comparisons (qualitative)

Outcome	Interventions or comparisons (total sample size)	Study	Findings	Quality
RCTs				
Acute GU ≥ Grade 3	EBRT (Long arm: 66 Gy in 33 fractions) (N=470) vs. EBRT (Short arm: 52.5 Gy in 20 fractions) (N=466)	Lukka (2005)	**Long arm is better**	B
	Conventional fractionation (N=50) vs. hypofractionation IMRT (N=50)	Pollack (2006)	No diff	B
Late GU ≥ Grade 3	EBRT (Long arm: 66 Gy in 33 fractions) (N=470) vs. EBRT (Short arm: 52.5 Gy in 20 fractions) (N=466)	Lukka (2005)	No diff	B
Retrospective cohort studies				
Acute GU ≥ Grade 3	Standard fractionation (N=74) vs. hypofractionation-3Gy/fraction (N=22) vs. hypofractionation-3.15Gy/fraction EBRT (N=34)	Leborgne (2008)	No diff	C
Late GU ≥ Grade 3	Standard fractionation (N=130) vs. hypofractionation EBRT (N=89)	Leborgne (2009)	No diff	B

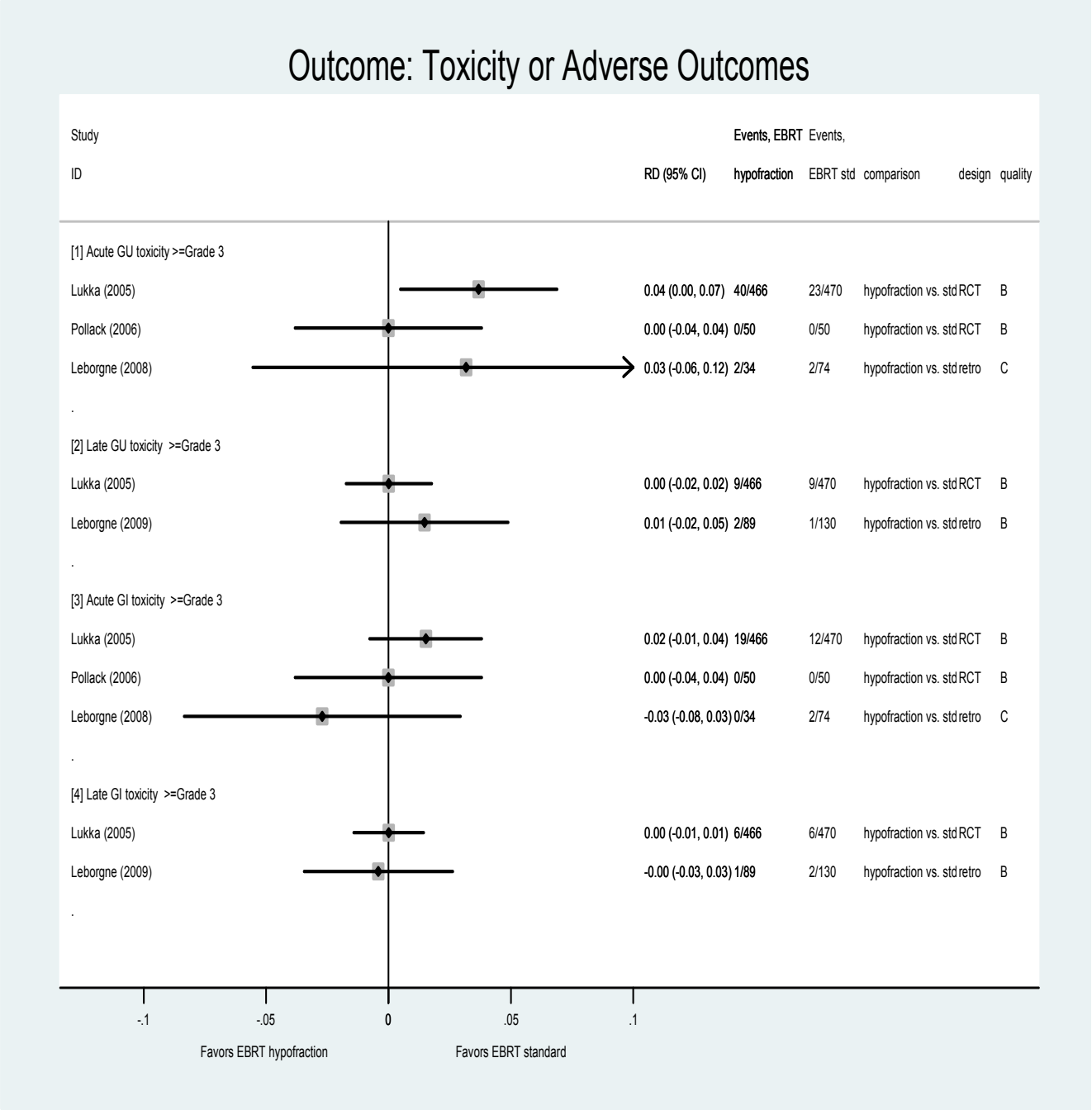
Better: statistically significant risk difference in increasing acute/late GI toxicity, comparing EBRT fraction sizes
No difference: no statistically significant risk difference in acute/late GI toxicity, comparing EBRT fraction sizes
Worse: statistically significant risk difference in decreasing acute/late GI toxicity, comparing EBRT fraction sizes
Bold words signify statistical significance $P<0.05$

Table E6. Gastrointestinal toxicity: EBRT fraction size comparisons (qualitative)

Outcome	Interventions or comparisons (total sample size)	Study	Findings	Quality
RCTs				
Acute GI ≥ Grade 3	EBRT (Long arm: 66 Gy in 33 fractions) (N=470) vs. EBRT (Short arm: 52.5 Gy in 20 fractions) (N=466)	Lukka (2005)	No diff	B
	Conventional fractionation (N=50) vs. hypofractionation IMRT (N=50)	Pollack (2006)	No diff	B
Late GI ≥ Grade 3	EBRT (Long arm: 66 Gy in 33 fractions) (N=470) vs. EBRT (Short arm: 52.5 Gy in 20 fractions) (N=466)	Lukka (2005)	No diff	B
Retrospective cohort studies				
Acute GI ≥ Grade 3	Standard fractionation (N=74) vs. hypofractionation-3Gy/fraction (N=22) vs. hypofractionation-3.15Gy/fraction EBRT (N=34)	Leborgne (2008)	No diff	C
Late GI ≥ Grade 3	Standard fractionation (N=130) vs. hypofractionation EBRT (N=89)	Leborgne (2009)	No diff	B

Better: statistically significant risk difference in increasing acute/late GI toxicity, comparing EBRT fraction sizes
No difference: no statistically significant risk difference in acute/late GI toxicity, comparing EBRT fraction sizes
Worse: statistically significant risk difference in decreasing acute/late GI toxicity, comparing EBRT fraction sizes
Bold words signify statistical significance $P<0.05$

Figure E4. Genitourinary and gastrointestinal toxicity: EBRT fraction size comparisons



Other Intra-EBRT Comparisons (Table E7)

Randomized controlled trials (RCTs) (Table E7)

One RCT compared EBRT using endorectal balloon for prostate immobilization with EBRT not using endorectal balloon.[47] All 48 patients received some form of ADTs. No data on T staging were reported. There were no differences in the acute genitourinary or gastrointestinal toxicity ≥ grade 3 in the two groups (no events in either group). In terms of chronic genitourinary toxicity ≥ grade 3 comparing EBRT with endorectal balloon versus without endorectal balloon, there were no events reported in either group. In terms of chronic gastrointestinal toxicity ≥ grade 3 comparing EBRT with endorectal balloon versus without endorectal balloon, it was 0% versus 4% (no P value reported). The methodological quality of this study was rated B because of suboptimal reporting.

Prospective studies (Table E7)

One prospective cohort compared patients who received conformal radiotherapy to the prostate only (CRT-PO) with patients who received whole pelvis and prostate boost radiotherapy (WP+PB).[48] Fifty one patients received CRT-PO and 46 received WP+PB. The CRT-PO group tended to be slightly older men (mean 70 years) with stage T1 or T2 disease with lower PSA values (median 9 ng/mL), lower Gleason scores (78% ≤ 7) who largely did not receive ADTs. The WP+PB group tended to have somewhat younger men (mean 67 years), with stage T2 or T3 disease, higher PSA values (median 16.5 ng/mL), higher Gleason scores (59% ≤ 7) and most received some form of ADTs (91%). The study reported radiation induced fatigue based on fatigue pictogram, questionnaire, and fatigue scale (range 0-44, 0 = best and 44 = worst). A significant number of patients reported some level of fatigue at baseline. The fatigue scale showed that those receiving WP+PB reported higher scores compared to CRT-PO (baseline: CRT-PO 3.3 vs. WP+PB 4.6; week 6: CRT-PO 4.2 vs. WP+PB 6.2). The methodological quality of this study was rated C. There was no statistical adjustment for potential confounders.

Retrospective studies (Table E7)

One retrospective cohort study evaluated the effect of different 3D-CRT nodal target coverage on biochemical failure-free survival (bFFS).[49] Of the 669 patients evaluated, 384 underwent mini pelvis (MP) field treatment (excluding common iliac nodes) and 285 underwent whole pelvis (WP) field treatment (including common iliac nodes). Some form of ADTs were used in 45% of the patients and 11% of the patients had stage T3 disease. This study observed that the pretreatment PSA level, Gleason score, T stage, and the use of ADT were predictors of treatment response. An increase in bFFS in the MP field arm compared to the WP field arm was observed on univariate analysis, but not on multivariate analysis when corrected for factors including age at diagnosis, pretreatment PSA level, Gleason score, T stage, ADT, total radiation dose, and year of radiation treatment (HR 0.94, 95% CI 0.66 to 1.33, P = 0.71). The methodological quality of this study was rated B.

One retrospective cohort study compared the effects of 3D-CRT versus 2D-CRT on anorectal function in 67 patients; the chronic grade ≥3 rectal toxicity at 2 years was 10% versus 8%, respectively.[50] The methodological quality of this study was rated C. There was no statistical adjustment for potential confounders.

Table E7. Characteristics of studies that compared other EBRT technique comparisons

Author Year [UI] Country	Intervention(s) or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobilization technique	Applied margins for PTV	Planning algorithm	Quality Comments
RCT														
Van Lin 2007 17161552 Netherlands	3D CRT with ERB	24	nd	nd	nd	nd	nd	100	67.5	2.25	Endorectal balloon	0.9cm	Pinnacle	B com-8
	3D CRT no ERB	24	nd	nd	nd	nd	nd	100	67.5	2.25		0.9cm	Pinnacle	
Prospective Cohort Study														
Danjoux 2007 17333296 Canada	Conformal radiotherapy	51	70.3	nd	98	9	5-6: 31 7: 47 8-10: 22	24	70-76	2	four-field conformal technique with an 18 MV photon beam	nd	nd	B
	Whole pelvis and prostate boost radiotherapy	46	67.4	nd	61	16.5	5-6: 8 7: 48 8-10: 43	91	whole pelvis: 45 Gy in 25 fractions prostate boost: 26 Gy in 13 fractions	1.8-2.0	four-field conformal technique with an 18 MV photon beam	nd	nd	
Retrospective Cohort Study														
Soto DE 2008 18308110 USA	EBRT (Whole pelvis 3D CRT)	384	70.3	nd	86	25.1	2-6: 31 7: 42 8-10: 27	37	71		nd	1-2 cm	nd	B
	EBRT (Mini Pelvis 3D CRT)	285	69.0	nd	92	16.5	2-6: 32 7: 43 8-10: 25	52	75		nd	1-2 cm	nd	

Author Year [UI] Country	Intervention(s) or comparison	N	Mean or Median, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobilization technique	Applied margins for PTV	Planning algorithm	Quality Comments
Yeoh 2009 18571336 Australia	EBRT (2D RT)	38	68	nd	nd	nd	nd	nd	55 / 64	2.75/2.0	nd	1.5 cm isodose margin	Pinnacle	C Com-1
	EBRT (3D RT)	29	71	nd	nd	nd	nd	nd	55 / 64	2.75/2.0	nd	1.5 cm isodose margin	Pinnacle	

com-1: No adjustment for potential confounders
com-2: incomplete reporting (e.g., little or no description of study eligibility criteria or methods, missing data)
com-3: historical comparison
com-4: incomplete statistical analysis (e.g., P value not reported)
com-5: different lengths of follow-up between groups
com-6: baseline participant characteristics not entirely comparable between groups (no adjustment)
com-7: loss to follow-up ≥20% (only for RCTs)
com-8: method of randomization not reported

Appendix F. Detailed results for intra-LDRBT comparisons

Intra-LDRBT comparisons (Tables F1-F3)

Randomized controlled trials (RCTs) (Table F1, F3)

One RCT compared I-125 (144 Gy) with Pd-103 (125 Gy) and reported three interim analyses on long-term morbidity and biochemical outcomes.[51-53] The number of patients reported in these three interim analyses ranged from 115 to 314. All the patients had either T1 or T2 disease. Less than 20 percent of the patients received some form of ADTs. Comparing I-125 with Pd-103, this trial reported that the freedom from biochemical failure at 3 years was 89% versus 91% (P = 0.76), and at 6 years it was 97% versus 99% (P = 0.15), respectively. This trial reported no significant difference between the two groups in the American Urological Association (AUA) Symptom Index at 2 years. This trial also noted a non-significant trend in more persistent rectal bleeding in the I-125 patients compared to the Pd-103 patients. The methodological quality of all 3 reports were rated B. Neither the patient nor the treating physician was blinded to the isotope used in the trial.

A second RCT compared LDRBT using I-125 (145 Gy) with LDRBT using I-125 (145 Gy) plus rectal protection with injection of hyaluronic acid.[56] All 69 patients had T1 or T2 disease. Up to 45% of the patients received some form of ADTs. Patients treated with rectal protection using hyaluronic acid had no macroscopic rectal bleeding, while 12% of patients without rectal protection had macroscopic rectal bleeding (P = 0.047). This was presumably assessed via patient questionnaire at the time of follow-up endoscopy (ranged from 13 to 24 months postimplant). The authors further stated that "no toxicity was produced from the hyaluronic acid or its injection". This study was rated B. No information was provided on the method of randomization.

Retrospective studies (Table F2)

Two retrospective analyses of the same sample reported the combined experience from 6 centers comparing different biological effective dose (BED) using I-125 or Pd-103 in which supplemental EBRT (22% of the patients) and short-term ADT was used (39%).[54, 55] The total sample size was 3,928. One percent of the patients had T3 disease. The BED being compared were <140 Gy, 140-200 Gy, and >200 Gy; the 10-year biochemical freedom from failure were 41%, 78%, 83% (P<0.0001, one way ANOVA), respectively. The study also analyzed 5-year biochemical freedom from failure by stratifying the BED dose into ≤ 220 Gy vs. > 220 Gy: in those patients with Gleason score 7, the rate was 84.2% vs. 89.5% (P = 0.073), respectively; in those with Gleason score 8 to 10, the rate was 48.8% vs. 85.7% (P = 0.05), respectively. The study also reported that in patients with PSA level > 20 ng/mL, a greater BED resulted in improved 5-year biochemical freedom from failure in the Gleason score 7 to 10 and 8 to 10 groups. Among patients with Gleason score 8-10, 5-year overall survival rate was significantly different across BED < 200 Gy, 200-220 Gy, and > 220 Gy groups (86.6% vs. 89.4% vs. 94.6%; P < 0.048). The methodological quality of this study was rated B. There was potential selection bias in this study as only those patients with dosimetry results (67%) were included.

Table F1. Characteristics of randomized controlled trials that compared different brachytherapy techniques

Author Year [UI] Country	Intervention(s) or comparison	N	Mean age, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobili-zation technique	Applied margins for PTV	Planning algorithm	Quality Comments
Herstein 2005 [16259869] US	LDRBT (I^{125})	159	65	nd	100	7: (1.9)	Range: 2-6	18	144Gy, TG 43	nd	nd	nd	nd	B com-8
	LDRBT (Pd^{103})	155	66	nd	100	6.7: (1.7)	Range: 2-6	17	125 Gy, NIST 99	nd	nd	nd	nd	
Merrick 2007 [17551297] US	LDRBT (I^{125})	127	64	nd	100	6.4: (1.7)	5.9: (0.3) [A]	Yes, nd%	125 Gy, TG 43	nd	nd	0.5 cm	AAPM TG-43 and update	B com-2, 8
	LDRBT (Pd^{103})	136	65	nd	100	6.7: (1.9)	6.0: (0.3) [A]	Yes, nd%	145 Gy, ABS-2000	nd	nd	0.5 cm	same as above	
Prada 2009 [19213607] 2009	LDRBT (I^{125}) with 6-8cc of hyaluronic acid	36	68	nd	100	8: (nd)	≤6: 97% 7: 3%	44	145 Gy, TG 43	nd	nd	nd	nd	C com-2, 8
	LDRBT (I^{125})	33	69	nd	100	8: (nd)	≤6: 92% 7: 8%	45	145 Gy, TG 43	nd	nd	nd	nd	
Wallner 2003 [14630265] US	LDRBT (I^{125})	57	65	nd	100	7.0: (1.9)	5.9: (0.24) [A]	16	144Gy, TG 43	nd	nd	nd	nd	B
	LDRBT (Pd^{103})	58	66	nd	100	6.7: (1.7)	5.9: (0.29) [A]	19	125 Gy, NIST 99	nd	nd	nd	nd	

[A] mean (SD)

com-1: No adjustment for potential confounders
com-2: incomplete reporting (e.g., little or no description of study eligibility criteria or methods, missing data)
com-3: historical comparison
com-4: incomplete statistical analysis (e.g., P value not reported)
com-5: different lengths of follow-up between groups
com-6: baseline participant characteristics not entirely comparable between groups (no adjustment)
com-7: loss to follow-up ≥20% (only for RCTs)
com-8: method of randomization not reported

Table F2. Characteristics of retrospective cohort studies that compared different brachytherapy techniques

Author Year [UI] Country	Intervention(s) or comparison	N	Mean age, yr	Race, %	T1 or T2, %	PSA (ng/mL), %	Gleason score, %	ADT, %	Total Dose (Gy)	Dose per fraction (Gy)	Immobilization technique	Applied margins for PTV	Planning algorithm	Quality Comments
Stone 2007 2009 [17689026, 18597953] US	biological effective dose (BED) <140 140-200, or >200 Gy [C]	3928	nd	nd	99	≤10: 76 10-20: 19: >20 5	≤6 73 7 22 8-10 6	62	nd	nd	nd	nd	nd	B

[C] 58% of patients had supplemental EBRT

com-1: No adjustment for potential confounders
com-2: incomplete reporting (e.g., little or no description of study eligibility criteria or methods, missing data)
com-3: historical comparison
com-4: incomplete statistical analysis (e.g., P value not reported)
com-5: different lengths of follow-up between groups
com-6: baseline participant characteristics not entirely comparable between groups (no adjustment)
com-7: loss to follow-up ≥20% (only for RCTs)
com-8: method of randomization not reported

Table F3. Urinary dysfunction: intra-LDRBT

Author Year [UI] Country	Outcome	Intervention	Follow-up, yr	No. Analyzed	Baseline	Change (SD)	Net difference	95%CI	P btw	Quality
Herstein 2005 [16259869] US	AUA score	LDRBT (I^{125})	2	151	7.6	1.2 (7.31)	+0.50	-1.16, 2.16	0.89	B
		LDRBT (Pd^{103})		145	8.2	0.7 (7.22)				

AUA score, AUA symptom index, American Urological Association symptom index (range, 0-35) in which higher scores indicate worse outcomes
This study was a RCT from Minnesota report.

Appendix G. Detailed results for Key Question 3

Key Question 3. How do specific patient characteristics, e.g., age, race/ethnicity, presence or absence of comorbidities, preferences (e.g., tradeoff of treatment-related adverse effects vs. potential for disease progression) affect the outcomes of these different forms of radiation therapy?

For this question, we evaluated only direct comparisons within studies. We did not make indirect cross-study comparisons. Patient-level characteristics are those that describe a patient's pre-procedure physical characteristics, prostate cancer characteristics, and other comorbid conditions.

Baseline risk (Table G1)

One long-term follow-up of an RCT[32] and four retrospective cohort studies[15, 22, 40, 54] evaluated different baseline risk as a potential modifying factor. Three studies categorized patients according to the National Comprehensive Cancer Network (NCCN) Guidelines risk stratification[32, 40, 54] and two were based on D'Amico stratification.[15, 22, 72] No consistent pattern of effect modification by baseline risk category was observed in these studies.

In the long-term follow-up of an RCT, the rate of 8-year freedom from clinical and/or biochemical failure was higher in the 78 Gy group than the 70 Gy group among low-risk (88% vs. 63%; P = 0.042) and high-risk patients (63% vs. 26%; P = 0.004), but no significant difference was noted in the intermediate-risk patients (86% vs. 76%; P = 0.36).[32]

In a retrospective cohort study with 16 years of follow-up, PSA relapse-free survival rates did not differ between radiation dosage groups (70.2, 75.6, 81, 86.4 Gy) among low-risk patients (quantitative data not provided); the rates were higher in the 75.6 Gy or 81 Gy group than 70.2 Gy or 86.4 Gy groups (HR: 0.71; P < 0.0001) in the intermediate risk group.[40] For high-risk patients, 5-year PSA relapse-free survival rates in 70.2 Gy, 75.6 Gy, 81 Gy, and 86.4 Gy groups were significantly different at 40%, 61%, 66%, and 71%, respectively (P < 0.0001). There were no differences in the rates of distant metastases free survival between different dosage groups among low-risk patients (quantitative data not provided); the rate was higher in the 81 Gy group than the 75.6 Gy groups among intermediate-risk patients (HR: 0.77; P = 0.04), and it was also higher in the 81 Gy group compared to the 70.2 Gy group among high-risk patients (HR: 0.83; P = 0.01).

A second retrospective cohort study reported that the five-year biochemical control rates did not differ among conventional dose 3D-CRT, high-dose IMRT, BT alone, and EBRT + BT groups among low- (92%, 93%, 97%, 100%, respectively; P = 0.298) and high-risk patients (55%, 76%, 50%, 100%, respectively; P = 0.184).[22] However, biochemical control rates were significantly better in high-dose IMRT, BT alone, or EBRT + BT group than conventional dose 3D-CRT group among intermediate-risk patients who did not receive ADT (85%, 83%, 100% vs. 65%, respectively; P = 0.0003). None of the patients in these comparisons received ADTs.

Two retrospective cohort studies reported no difference in treatment outcomes among baseline risk categories. In the study that examined three biologically effective dosages of BT, rates of biochemical freedom from failure were significantly increased with increasing dosages (< 140 Gy, 140-200 Gy, > 200 Gy) in all risk categories (low risk: 49.8% vs. 85.2% vs. 88.3%; P

< 0.0001; intermediate risk: 23.1% vs. 77.7% vs. 88.8%; P < 0.0001; high risk: 41.7% vs. 53.2% vs. 69.6; P < 0.0001). [54] In the other study, 10-year disease specific survival rates were higher in the EBRT group than the observation group, although statistical significance was not reported (low risk: 93% vs. 90%; intermediate risk: 88% vs. 81%; high risk: 80% vs. 70%; P value not reported).[15]

Gleason Score

One retrospective study found that across three dosages of BT (< 200 Gy, 200-220 Gy, > 220 Gy), rates of biochemical freedom from failure were significantly different among patients with baseline Gleason score of 8-10 (51.6% vs. 85.5%, vs. 90%; P < 0.001), but not among patients with Gleason score of 7 (82.3% vs. 82.5% vs. 89.5%; P = 0.09).[55]

Baseline PSA concentration

One long-term follow-up study of an RCT found a greater difference in the 8-year freedom from clinical and/or biochemical failure rate between the 78 Gy and the 70 Gy groups among patients with baseline PSA >10 ng/mL (78% vs. 39%; P < 0.001) than in patients with baseline PSA ≤ 10 ng/mL (78% vs. 66%; P = 0.24).[32] Among patients with baseline PSA >10 ng/ml, the rate of freedom from distant metastasis was higher in the 78 Gy group compared with the 70 Gy group, but statistical significance was not reached (98% vs. 88%; P = 0.056).[33] Among patients with baseline PSA ≤ 10 ng/ml, one patient in the 78 Gy group had distant metastasis while no patient in the 70 Gy group did (quantitative data not reported).[33]

Interaction of baseline risk category and PSA concentration

The interaction of baseline risk category and PSA concentrations was also evaluated in the above study. [32] Among intermediate- or high-risk patients, rates of freedom from clinical and/or biochemical failure at 8 years were significantly different between 78 Gy and 70 Gy among patients with baseline PSA >10 ng/mL, but not different among patients with baseline PSA ≤ 10 ng/mL (quantitative data not provided); no such difference was observed among low-risk patients.

Table G1. Effects of patient characteristics on treatment outcomes of different radiation therapies

Author Year [UI]	Treatment comparison	Analysis by factor of interest	Quality
Baseline risk on biochemical failure			
Albertsen 2007 [17296379]	EBRT vs. observation	Low risk – ▲survival rate in EBRT (P value not reported) Intermediate risk – ▲survival rate in EBRT (P value not reported) High risk - ▲survival rate in EBRT (P value not reported)	B
Kuban 2008 [17765406]	3D-CRT 78 Gy vs. 70 Gy	Low risk – ▲FFF in 78 Gy (P = 0.042) Intermediate risk – no difference High risk – ▲FFF in 78 Gy (P = 0.004)	B
Stone 2007 [17689026]	BT < 140 Gy, 140-200 Gy, > 200 Gy	Low risk - ▲FFF in higher dose (P < 0.0001) Intermediate risk - ▲FFF in higher dose (P < 0.0001) High risk - ▲FFF in higher dose (P < 0.0001)	B
Wong 2009 [19670452]	conventional dose 3D-CRT, high-dose IMRT, BT alone, or EBRT + BT	Low risk – no difference Intermediate risk – FFF: conventional dose 3D-CRT< BT alone < high-dose IMRT < EBRT + BT (P = 0.0003) High risk – no difference	B
Zelefsky 2008 [18280056] (452)	3D-CRT or IMRT 70.2, 75.6, 81, 86.4 Gy	Low risk– no difference Intermediate risk– ▲ PSA-relapse free survival in the 75.6 Gy or 81 Gy group compared with 70.2 Gy or 86.4 Gy groups (P < 0.0001); ▲rate of distant metastases free survival in 81 Gy compared with 75.6 Gy (P = 0.04) High risk– ▲ PSA-relapse free survival with ▲dose (P < 0.0001); ▲rate of distant metastases free survival in 81 Gy compared with 70.2 Gy (P = 0.01)	B
Baseline PSA concentration			
Kuban 2008 [17765406] Pollack 2002 [2128107]	3D-CRT 78 Gy vs. 70 Gy	PSA >10 ng/ml – ▲FFF in 78 Gy (P < 0.001); no difference in rate of distant metastases free survival PSA ≤ 10 ng/ml – no difference	B
Gleason Score			
Stone 2009 [18597953]	BT < 200 Gy, 200-220 Gy, >220 Gy	score 7 – no difference score 8-10 - ▲FFF with ▲dose (P < 0.001)	B
Interaction between baseline risk category and baseline PSA concentration			
Kuban 2008 [17765406] Pollack 2002 [2128107]	3D-CRT 78 Gy vs. 70 Gy	The difference in treatment between patients with PSA >10 ng/ml and patients with PSA <10 ng/ml was present among intermediate- and high-risk patients, but not among low-risk patients.	B

FFF: freedom from failure rate

Appendix H. CyberKnife® and related studies

We searched MEDLINE® on 1/12/2010 specifically for studies on prostate cancer treatment with CyberKnife®. We identified 15 studies, only one qualified for inclusion in our review. We also searched clinicaltrials.gov on 2/9/2010 and identified seven studies on CyberKnife® and prostate cancer registered on the clinicaltrials.gov website, one of them has been completed (NCT00855647) but the study results have not yet been publicly posted (http://clinicaltrials.gov/ct2/results?term=CyberKnife&pg=2).

Table H1. Studies on prostate cancer treatment with CyberKnife® (MEDLINE® on 1/12/2010)

Study	Title & Reference	Reason for exclusion
Fuller 2008 18374232	Virtual HDR CyberKnife treatment for localized prostatic carcinoma: dosimetry comparison with HDR brachytherapy and preliminary clinical observations. International Journal of Radiation Oncology, Biology, Physics. 2008;70:1588-1597	No comparative clinical outcome
Hossain 2008 18841856	Simulated real time image guided intrafraction tracking-delivery for hypofractionated prostate IMRT. Medical Physics. 2008;35:4041-4048	No clinical outcome
King CR 2003 12625751	CyberKnife radiotherapy for localized prostate cancer: rationale and technical feasibility. Technology in Cancer Research & Treatment. 2003;2:25-30	No clinical outcome
Pawlicki 2007 17472885	Investigation of linac-based image-guided hypofractionated prostate radiotherapy. Medical Dosimetry. 2007;32-71-79	No clinical outcome
Xie 2008 18722274	Intrafractional motion of the prostate during hypofractionated radiotherapy. International Journal of Radiation Oncology, Biology, Physics. 2008;72:236-246	No clinical outcome
Friedland 2009 19754215	Stereotactic body radiotherapy: an emerging treatment approach for localized prostate cancer. Technology in Cancer Research & Treatment. 2009;8:387-392	Single cohort study
King 2009 18755555	Stereotactic body radiotherapy for localized prostate cancer. Interim results of a prospective phase II clinical trial. International Journal of Radiation Oncology, Biology, Physics. 2009;73:1043-1048	Single cohort study (likely related to NCT00855647 listed above)
de CR 2006 17035061	Prostate localization systems for prostate radiotherapy. [Review][French] Cancer Radiotherapie. 2006:10:394-401	Review
de CR 2009 19211367	Image-guided radiotherapy: rational, modalities and results. [French] Bulletin du Cancer. 2009; 96:123-132	Review
Pawlicki 2007 17641522	Prostate cancer therapy with stereotactic body radiation therapy. [Review] Frontiers of Radiation Therapy & Oncology. 2007;40:395-406	Review
Thariat 2009 19736172	Current indications and ongoing clinical trials with CyberKnife stereotactic radiotherapy in 2009. [French] Bulletin du Cancer 2009; 96:853-864	Review
King 2009 19147028	Testicular dose from prostate CyberKnife: a cautionary note. International Journal of Radiation Oncology, Biology, Physics.	Commentary

	2009;73:636-637	
Vikram 2009 19735890	In regard to King et al. (Int J Radiat Oncol boil Phys 2009;73:1043-1048). International Journal of Radiation Oncology, Biology, Physics. 2009;75:632	Commentary
Yeager 2009 19147032	Accuray company advertising successful prostate cancer treatments with CyberKnife. International Journal of Radiation Oncology, Biology, Physics. 2009;73:638-639	Commentary
Hannoun-Levi 2007 17888705	Robotic radiotherapy for prostate cancer with CyberKnife [French]. Cancer Radiotherapie. 2007;11:476-482	Discussion

Table H2. Additional studies from 2007-2009 on stereotactic body radiation therapy for prostate cancer identified from MEDLINE® on 12/30/2010 that did not qualify for inclusion in this review

Study	Title & Reference	Reason for exclusion
Madsen 2007 17336216	Stereotactic hypofractionated accurate radiotherapy of the prostate (SHARP), 33.5 Gy in five fractions for localized disease: first clinical trial results. International Journal of Radiation Oncology, Biology, Physics. 67(4):1099-105, 2007 Mar 15.	Single cohort study
Chang 2007 18091059	Stereotactic body radiation therapy: a comprehensive review. American Journal of Clinical Oncology. 30(6):637-44, 2007 Dec.	Review
Lo 2010 19997074	Stereotactic body radiation therapy: a novel treatment modality. Nature Reviews Clinical Oncology. 7(1):44-54, 2010 Jan.	Review

Table H3. Additional studies from 2007-2009 on High Dose Rate Brachytherapy for prostate cancer identified from MEDLINE® on 12/30/2010 that did not qualify for inclusion in this review

Study	Title & Reference	Reason for exclusion
Kim 2007 18449148	Measurement of craniocaudal catheter displacement between fractions in computed tomography-based high dose rate brachytherapy of prostate cancer. Journal of Applied Clinical Medical Physics 8 (4):2415. 2007.	No clinical outcome
Morton 2008 18037356	A comparison of anatomy-based inverse planning with simulated annealing and graphical optimization for high-dose-rate prostate brachytherapy. Brachytherapy 7 (1):12 -6. 2008;-Mar.	No clinical outcome
Nilsson 2008 17980507	Is the use of a surrogate urethra an option in prostate high-dose-rate brachytherapy? International Journal of Radiation Oncology, Biology , Physics 71 (1):36 -40 . 2008.	No clinical outcome
Das 2007 18044301	Thermoluminescence dosimetry for in-vivo verification of high dose rate brachytherapy for prostate cancer. Australasian Physical & Engineering Sciences in Medicine 30 (3):178 -84 . 2007.	Single cohort study

Ghadjar 2009 19038584	Toxicity and early treatment outcomes in low- and intermediate-risk prostate cancer managed by high-dose-rate brachytherapy as a monotherapy. Brachytherapy 8 (1):45 -51. 2009;-Mar.	Single cohort study
Konishi 2009 19345517	Correlation between dosimetric parameters and late rectal and urinary toxicities in patients treated with high-dose-rate brachytherapy used as monotherapy for prostate cancer. International Journal of Radiation Oncology, Biology, Physics 75 (4):1003 -7 . 2009.	Single cohort study
Yoshida 2007 17606414	New implant technique for separation of the seminal vesicle and rectal mucosa for high-dose-rate prostate brachytherapy. Brachytherapy 6 (3):180 -6. 2007;-Sep.	Single cohort study
Corner 2008 18249501	A Phase II study of high-dose-rate afterloading brachytherapy as monotherapy for the treatment of localized prostate cancer. International Journal of Radiation Oncology, Biology, Physics 72 (2):441 -6. 2008.	Did not meet our inclusion criteria
Hoskin 2008 18755623	[Review] [9 refs]. Cancer Radiotherapie 12 (6 -7):512 -4. 2008.	Review

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