Cancer Treatment Reviews 48 (2016) 50–60

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Hot Topic

Comparison of outcomes and toxicities among radiation therapy treatment options for prostate cancer

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ARTICLE INFO

Article history:
Received 2 April 2016
Received in revised form 7 June 2016
Accepted 8 June 2016

Keywords:
Comparative effectiveness research
Prostate cancer
Technology
Personalized medicine
Radiation therapy
Quality of life
Clinical trials
Brachytherapy
Proton therapy

ABSTRACT

We review radiation therapy (RT) options available for prostate cancer, including external beam (EBRT; with conventional fractionation, hypofractionation, stereotactic body RT [SBRT]) and brachytherapy (BT), with an emphasis on the outcomes, toxicities, and contraindications for therapies. PICOS/PRISMA methods were used to identify published English-language comparative studies on PubMed (from 1980 to 2015) that included men treated on prospective studies with a primary endpoint of patient outcomes, with $\geqslant$70 patients, and $\geqslant$5 year median follow up. Twenty-six studies met inclusion criteria; of these, 16 used EBRT, and 10 used BT. Long-term freedom from biochemical failure (FFBF) rates were roughly equivalent between conventional and hypofractionated RT with intensity modulation (evidence level 1B), with 10-year FFBF rates of 45–90%, 40–60%, and 20–50% (for low-, intermediate-, and high-risk groups, respectively). SBRT had promising rates of BF, with shorter follow-up (5-year FFBF of >90% for low-risk patients). Similarly, BT (5-year FFBF for low-, intermediate-, and high-risk patients have generally been >85%, 69–97%, 63–80%, respectively) and BT + EBRT were appropriate in select patients (evidence level 1B). Differences in overall survival, distant metastasis, and cancer specific mortality (5-year rates: 82–97%, 1–14%, 0–8%, respectively) have not been detected in randomized trials of dose escalation or in studies comparing RT modalities. Studies did not use patient-reported outcomes, through Grade 3–4 toxicities were rare (<5%) among all modalities. There was limited evidence available to compare proton therapy to other modalities. The treatment decision for a man is usually based on his risk group, ability to tolerate the procedure, convenience for the patient, and the anticipated impact on quality of life. To further personalize therapy, future trials should report (1) race; (2) medical comorbidities; (3) psychiatric comorbidities; (4) insurance status; (5) education status; (6) marital status; (7) income; (8) sexual orientation; and (9) facility-related characteristics.

Introduction

Prostate cancer is the most prevalent cancer diagnosed in men in the United States, aside from skin cancer [1]. Treatment options for non-metastatic prostate cancer typically include active surveillance (AS), radical prostatectomy (RP) and radiation therapy (RT) [2]. Within RT, treatment options include (1) external beam radiation therapy (RT), which may be conventionally fractionated (CFRT) with intensity modulated radiation therapy (IMRT) or protons, hypofractionated RT (HFRT) with IMRT or protons, or delivered as stereotactic body RT (SBRT); and (2) brachytherapy (BT), either high dose rate (HDR-BT) or low dose rate (LDR-BT). For reference, we define the various forms of RT in the Glossary. Although there are many standard treatment options for prostate cancer, randomized clinical trials (RCTs) to define the optimal therapy for patients with localized or locally advanced disease are limited [3].

In modern medicine, it is crucial for primary care physicians and specialists (including oncologists) to work together to provide consistent, accurate information to patients regarding treatment options for prostate cancer. The goal of this systematic review article is to provide an understanding of the evolving definitive RT options available for prostate cancer by (1) comparing RT fractionation regimens (including external beam RT and brachytherapy) and applicability to risk groups; (2) comparing and contrasting outcomes, toxicities, and contraindications of the approaches; and (3) discussing future implications of these approaches and

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http://dx.doi.org/10.1016/j.ctrv.2016.06.006
0305-7372/

how they integrate into active surveillance. For the purposes of this review article, we do not include outcomes data on other treatments for localized prostate cancer, including RP, post-RP RT (e.g. in the adjuvant or salvage setting), or high intensity focused ultrasound. Since the choice of a patient for RT instead of RP is sometimes due to presence of comorbidities or age, we briefly juxtapose the appropriateness, contraindications, and toxicities of adjuvant/salvage RT.

Methods

Key Questions

We focused on three Key Questions:

(1) What is the effectiveness of various forms of RT (e.g. conventionally fractionated RT ± IMRT, hypofractionated RT ± IMRT, SBRT, LDR-BT, HDR-BT), in terms of prostate cancer control outcomes, for clinically localized prostate cancer?
(2) What is the effectiveness of various forms of RT (e.g. conventionally fractionated RT ± IMRT, hypofractionated RT ± IMRT, SBRT, LDR-BT, HDR-BT), in terms of toxicities, for clinically localized prostate cancer?
(3) Based on the outcomes and toxicities, what should practitioners consider when discussing a particular type of RT with prostate cancer patients?

Data sources and searches

Three researchers searched the published English medical literature from 1980 through 2015 in MEDLINE and PubMed for full-text manuscripts (excluding abstracts) using the terms "prostate cancer," and "radiation therapy," along with any of the following: "external beam radiation therapy," "hypofractionated radiation therapy," "proton beam," "stereotactic body radiation therapy," "high dose rate brachytherapy," and "low dose rate brachytherapy." Terms were in titles or MeSH headings. The initial search resulted in 1558 articles.

Study selection

We defined inclusion criteria for the literature search using the Population, Intervention, Control, Outcome, Study (PICOS) design approach (Table 1). We conducted a systematic search using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) literature selection process (Fig. 1) [4]. Three authors searched reference lists of identified papers to supplement the literature search.

Patient populations of interest

We included studies of men with organ-confined (T1-T2, N0-Nx, M0) and locally advanced (T3-T4, N0-Nx, M0) prostate cancer, regardless of age, histologic grade, or PSA level. T-stage alone is a poor prognosticator, and >90% of patients are T1c and T2; thus, risk groups were defined by NCCN classification, the preferred prognostication system [5].

We omitted studies comparing RT to RP and studies evaluating adjuvant and salvage RT post-RP for several reasons. First, our goal was to compare RT fractionation regimens, source types (i.e. external beam vs. brachytherapy), techniques (i.e. conformal vs. intensity modulation), and particle (i.e. photon vs. proton). Second, there is limited data comparing contemporary forms of RP (e.g. robotic, laparoscopic approaches) to contemporary forms of RT (i.e. RP vs. IMRT, RP vs. SBRT, RP vs. HDR-BT), particularly with controlling for the use of androgen deprivation therapy (ADT). Third, for patients with obstructive symptoms (either from tumor bulk or urinary comorbidities), initial therapy with RP (with or without adjuvant/salvage RT) may be most appropriate, and this should be considered for individual cases. Fourth, recommendations regarding adjuvant and salvage RT after RP have been published [6].

Intervention and control

The intervention was BT or external beam RT as definitive therapy. An included study may have multiple arms that contains the intervention vs. another form of RT (e.g. external beam RT vs. BT); or it may be a single-arm study of external beam RT or BT focusing on dose escalation. We organize studies for our discussion

Table 1
PICOS: participants, interventions, comparisons, outcomes, and study design.

Population	Men with localized (T1-T2, N0-Nx, M0) and locally advanced (T3-T4, N0-Nx, M0) prostate cancer				
Intervention	Definitive brachytherapy: either high-dose rate (HDR) or low-dose rate (LDR) into the prostate Definitive external beam radiation therapy (EBRT), using conventional fractionation, hypofractionation, stereotactic body radiation therapy, or proton therapy				
Control	Multi-arm study that contains the intervention vs. another form of RT (e.g. EBRT vs. brachytherapy); or single-arm study of either				
Outcomes					
Efficacy	Clinical (surrogate outcomes) for all studies: • Freedom from biochemical failure, the time from which therapy for prostate cancer occurs until a rise in PSA hits a predefined threshold, as defined by Phoenix (i.e. nadir + 2ng/mL) or ASTRO (3 consecutive rises) definitions • Patient and study-specific: overall survival, cancer specific survival, distant metastasis				
Safety	Late RTOG genitourinary and gastrointestinal toxicities				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Genitourinary	None	Slight epithelial atrophy Minor telangiectasia (microscopic hematuria)	Moderate frequency Generalized telangiectasia Intermittent macroscopic hematuria	Severe frequency and dysuria Severe generalized telangiectasia (often with petechiae) Frequent hematuria Reduction in bladder capacity (<150 cc)	Necrosis/Contracted bladder (capacity <100 cc) Severe hemorrhagic cystitis
Gastrointestinal	None	Mild diarrhea Mild cramping Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic Bowel movement >5 times daily Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/perforation Fistula
Study design					
Efficacy and/or safety	Prospective studies only; ⩾70 patients; one or more arms; ⩾5 y median follow-up; ⩾5 y actuarial follow-up				

Abbreviations: ASTRO, American Society of Therapeutic Radiology and Oncology; PSA, prostate specific antigen; RT, radiation therapy.