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Review Article

American Brachytherapy Society Task Group Report: Use of androgen deprivation therapy with prostate brachytherapy—A systematic literature review

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ABSTRACT

PURPOSE: Prostate brachytherapy (PB) has well-documented excellent long-term outcomes in all risk groups. There are significant uncertainties regarding the role of androgen deprivation therapy (ADT) with brachytherapy. The purpose of this report was to review systemically the published literature and summarize present knowledge regarding the impact of ADT on biochemical progression-free survival (bPFS), cause-specific survival (CSS), and overall survival (OS).

METHODS AND MATERIALS: A literature search was conducted in Medline and Embase covering the years 1996−2016. Selected were articles with >100 patients, minimum followup 3 years, defined risk stratification, and directly examining the role and impact of ADT on bPFS, CSS, and OS. The studies were grouped to reflect disease risk stratification. We also reviewed the impact of ADT on OS, cardiovascular morbidity, mortality, and on-going brachytherapy randomized controlled trials (RCTs).

RESULTS: Fifty-two selected studies (43,303 patients) were included in this review; 7 high-dose rate and 45 low-dose rate; 25 studies were multi-institutional and 27 single institution (retrospective review or prospective data collection) and 2 were RCTs. The studies were heterogeneous in patient population, risk categories, risk factors, followup time, and treatment administered, including ADT administration and duration (median, 3−12 months);71% of the studies reported a lack of benefit, whereas 28% showed improvement in bPFS with addition of ADT to PB. The lack of benefit was seen in low-risk and favorable intermediate-risk (IR) disease and most high−dose rate studies. A bPFS benefit of up to 15% was seen with ADT use in patients with suboptimal dosimetry, those with multiple adverse risk factors (unfavorable IR [uIR]), and most high-risk (HR) studies. Four studies reported very small benefit to CSS (2%). None of the studies showed OS advantage; however, three studies reported an absolute 5−20% OS detriment with ADT. Literature suggests that OS detriment is more likely in older patients or those with pre-existing cardiovascular disease. Four RCTs with an adequate number of patients and well-defined risk stratification are in progress. One RCT will answer the question regarding the role of ADT with PB in favorable IR patients and the other three RCTs will focus on optimal duration of ADT in the uIR and favorable HR population.

CONCLUSIONS: Patients treated with brachytherapy have excellent long-term disease outcomes. Existing evidence shows no benefit of adding ADT to PB in low-risk and favorable IR patients. UIR and HR patients and those with suboptimal dosimetry may have up to 15% improvement in bPFS with addition of 3−12 months of ADT, with uncertain impact on CSS and a potential detriment on OS. To minimize morbidity, one should exercise caution in prescribing ADT together with PB, in

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particular to older men and those with existing cardiovascular disease. Due to the retrospective nature of this evidence, significant selection, and treatment bias, no definitive conclusions are possible. RCT is urgently needed to define the potential role and optimal duration of ADT in uIR and favorable HR disease.

Keywords: Prostate cancer; Brachytherapy; Androgen deprivation therapy; Outcomes; bPFS; CSS; OS

Introduction

Having emerged in the dawn of the prostate-specific antigen (PSA) era, prostate brachytherapy (PB) has gained worldwide acceptance and is currently considered a standard treatment for organ confined prostate cancer (PCa). Excellent long-term results have been published for all risk groups (1). Despite a large body of retrospective and prospective single- or multi-institutional data, significant uncertainties remain regarding the role of androgen deprivation therapy (ADT), external beam radiation (EBRT) or both, in patients treated with PB both with low-dose rate (LDR) and high-dose rate (HDR), particularly for intermediate-risk (IR) and high-risk (HR) PCa. Data from prospective randomized control trials will not be available for several years.

The purpose of this article was to review the published literature systematically and to summarize present knowledge regarding the role of ADT with PB. Clinical trials will be reviewed and future directions for research outlined. The mechanism of interaction between ADT and radiation, adverse effects, and impact on cardiovascular morbidity, mortality, and overall survival (OS) will be described. We separately considered the effects of ADT on biochemical progression-free survival, (bPFS), cause-specific survival (CSS), and OS in low-risk (LR) IR and HR group stratification. We considered both LDR and HDR retrospective institutional and multi-institutional studies, reviewed the limited data on this subject available from randomized controlled trials (RCTs), and reviewed on-going RCTs. We summarize the current available clinical evidence regarding the use of ADT with PB and provided recommendations regarding its use.

Methods and materials

A literature search was conducted in Medline and Embase covering the years 1996−2016. We searched articles on ADT searching under the subject heading ‘‘androgen deprivation therapy’’ in Embase and searching the titles of articles in Medline for the words ‘‘androgen’’ and ‘‘depriv*’’; 814 articles were identified; those directly focused on toxicity or the use of ADT and PB were reviewed in great detail ($n = 247$). Outcome articles were cross-referenced with the systematic outcome analysis (1) and the systematic review of randomized trials in PCa (2); 52 were selected for this review, all with >100 patients, with clearly defined risk stratification and directly examining the role and impact of ADT on primarily bPFS, in addition to CSS and OS where available. Excluded were those with followup of <3 years, those where no ADT was given, or where data required could not be extracted (e.g., studies where results between PB and EBRT alone were compared, but effect of ADT on clinical outcomes was assessed together for PB, and non-PB cohorts) (Fig. 1). Factors predictive of bPFS, CSS, and OS were extracted from multivariable analysis (MVA) in 50 of 52 articles and are included in the tables.

American Brachytherapy Society, American College of Radiology, American Society for Radiation Oncology, European Society for Radiotherapy and Oncology/ European Association of Urology/European Organization for Research and Treatment of Cancer, and National Comprehensive Cancer Network recommendations regarding use of ADT with PB

Most of the earlier mentioned best practice guideline recommendations underline the controversy regarding use of ADT and PB and do not give firm recommendations apart from recommending ADT for downsizing. For example, American Brachytherapy Society recommends no ADT in LR and its use in IR is optional and more strongly recommended in HR (3). American Brachytherapy Society recommendations for HDR do not refer to use of ADT with HDR, apart from recommending ADT for downsizing (4). American College of Radiology similarly states that the use of ADT is ‘‘usually not appropriate’’ for LR disease, ‘‘may be appropriate’’ for IR disease, and is ‘‘usually appropriate’’ for HR disease (5); 2016 National Comprehensive Cancer Network (NCCN) guidelines do not recommend ADT for IR treated with PB. For HR disease, ADT ‘‘may or may not be used’’ together with EBRT and PB boost and duration is specified between 0 and 36 months (6). European Society for Radiotherapy and Oncology/European Association of Urology/European Organization for Research and Treatment of Cancer (7), Groupe Europeen de Curetherapie/European Society for Radiotherapy and Oncology-European Association of Urology (8), and American Society for Radiation Oncology (9) have no specific recommendation or mention the use of ADT with PB.

ADT in PCa

In 1940, Canadian-born Charles Huggins recognized the androgen dependence of PCa. In 1966, he was awarded the