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Brachytherapy ■ (2017) ■

BRACHYTHERAPY

High–intermediate prostate cancer treated with low-dose-rate brachytherapy with or without androgen deprivation therapy

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ABSTRACT

PURPOSE: To describe outcomes of men with unfavorable (high-tier) intermediate risk prostate cancer (H-IR) treated with low-dose-rate (LDR) brachytherapy, with or without 6 months of androgen deprivation therapy (ADT).

METHODS AND MATERIALS: Patients with H-IR prostate cancer, treated before 2012 with LDR brachytherapy without external radiation are included. Baseline tumor characteristics are described. Outcomes between groups receiving ADT are measured by Phoenix (nadir +2 ng/mL), and threshold 0.4 ng/mL biochemical relapse definitions (bNEDs), as well as clinical end points. Standard descriptive and actuarial statistics are used.

RESULTS: Two hundred sixty men were eligible, 139 (53%) did not receive ADT and 121 (47%) did. Median follow-up was 5 years. Men treated with ADT had higher T stage and percent positive cores but lower pathologic grade group. bNED rates with and without ADT at 5 years are 86% and 85% ($p = 0.52$) with the Phoenix definition, and 83% and 78% ($p = 0.13$) with the threshold definition. Local recurrence or metastasis were rare in both groups (<5%, p = not significant). Death from prostate cancer only occurred in 4 patients, 2 in each group. Overall survival was 85% in those treated with ADT and 93% without at 8 years, $p = 0.15$.

CONCLUSIONS: The addition of 6 months of ADT to LDR brachytherapy for H-IR prostate cancer does not improve 5 year prostate specific antigen control, and we no longer routinely recommended it.

Keywords: Low-dose-rate; Androgen deprivation therapy; Biochemical control; Intermediate risk; Prostate cancer; Brachytherapy

Introduction

The very high cure rates obtained with low-dose-rate (LDR) brachytherapy in men with favorable risk prostate cancer has encouraged its use in those with higher risk disease. The intermediate risk (IR) group is heterogeneous, and several authors have suggested that it should be divided into favorable and unfavorable, based on the number of adverse risk factors (1). The Canadian ProCars project (2) used a large database of over 7000 men treated with external beam radiation therapy (EBRT) or brachytherapy to define two subgroups: low intermediate (L-IR) and high intermediate (H-IR). Men with H-IR are distinguished by having a prostate specific antigen (PSA) >10 ng/ml plus either a Gleason score of 7, or stage T2b/c. These men have outcomes that are closer to those with high-risk cancer when treated with EBRT (2).

Outcomes of men with IR cancer treated with EBRT are improved by the addition of androgen deprivation therapy (ADT) (3, 4). However it is unknown whether the benefit of ADT is apparent only with lower doses of radiation. The NRG/RTOG 0815 trial (5) is currently exploring whether 6 months of ADT improves outcomes when higher doses of radiation are used, either by means of an EBRT or a brachytherapy boost.

Received 13 July 2017; received in revised form 6 August 2017; accepted 8 August 2017.

Conflicts of interest: Dr Pickles reports personal fees from Abbvie, Astra-Zeneca, Astellas, Bayer, Ferring Pharma, and Jansen pharmaceuticals and grants from GlaxoSmithKline and Sanofi, outside the submitted work. Dr Morris and Dr Keyes have nothing to disclose.

Financial disclosure: The authors declared no financial disclosures.

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1538-4721/$ - see front matter
http://dx.doi.org/10.1016/j.brachy.2017.08.003

The BC Cancer Agency (BCCA) brachytherapy program starting treating men with H-IR cancer as a standard option in 2005. Due to concerns about the potential risks of ADT (6), and in view of very low relapse rates observed with L-IR cancer, the use of adjuvant ADT was left to physician discretion. Approximately half of those treated with H-IR cancer received ADT. In this report, we describe the outcomes (biochemical relapse, metastasis, and survival) of men with H-IR cancer treated with or without 6 months of ADT, in combination with LDR brachytherapy, without supplemental EBRT.

Methods and materials

The BCCA prostate brachytherapy program maintains a prospective patient database that includes baseline prognostic information, treatment-related data, as well as biochemical and clinical outcomes. It was established at the start of our brachytherapy program in 1998 and now contains records of over 6000 cases. Only patients treated before 2012 were included so as to achieve a median follow-up of 5 years.

Between 1998 and December, 2011, a total of 3841 patients were treated with brachytherapy at the BCCA. Patients are selected who had H-IR prostate cancer, defined as a baseline PSA of >10 plus either Gleason score 7 or T2b/c cancer, without external beam radiation therapy (n = 273). Thirteen were excluded who reside outside of British Columbia (n = 12), as their follow-up is under the care of referring physicians and follow-up information may be incomplete, and 1 patient who received noncastrating cytoreduction with dutasteride and bicalutamide. The final data set comprises 260 cases. The decision to use ADT was made by the Radiation Oncologist in consultation with the patient, taking into account his tumor risk factors, comorbidities, and preferences.

Outcomes information is collected at each patient visit, scheduled for 6 weeks, then six monthly thereafter. PSA patterns suggestive of a bounce or failure are audited, and either a "bounce over" date or PSA failure date is recorded. The Phoenix nadir +2 definition of PSA relapse is used (7), with "unfailing" of relapse where PSA bounces resolve spontaneously with a PSA level falling to <0.5 ng/mL, as in prior publications (8). Secondary PSA relapse using a threshold definition of 0.4 ng/mL is also calculated; for this definition, a bounce is "unfailed" if the PSA falls to less than 0.4 ng/mL without intervention. PSA value at last follow-up (minimum 4 years posttreatment) is reported for those who have not had a biochemical relapse, and PSA doubling time is calculated for all those with a rising PSA level, whether or not a relapse has occurred. Patients who have relapsed are assessed and offered prostate biopsy, and other investigations such as bone and CT scans were indicated.

Brachytherapy techniques have been described previously (8).In brief, we use transrectal ultrasound preplanning and a modified Seattle seed distribution, with the intent of delivering a prescribed peripheral mean dose of 144 Gy, while keeping V150 less than 65% and V200 under 20%. All patients have postoperative dosimentry, usually the same day with CT alone, or at day 30 with MR-CT fusion. A quality assurance (QA) committee oversees the program quality metrics and arranges twice-annual educational QA meetings (9).Random cases are sent to each of the 18 physicians currently credentialed and performing prostate brachytherapy for peer review of contours and postoperative dosimetry. Weekly or twice-monthly QA meetings are held to review upcoming cases and recent implants. Patients with poor dosimetry are considered for a revision implant (10).

Database quality is maintained by cross-reference against other institutional data sources. For this analysis, cause and date of death was checked with the provincial death registry, and ADT use is checked against the BCCA pharmacy database. Logical checks of testosterone level against ADT use and clinical event with PSA relapse (such as death ascribed to prostate cancer in the absence of metastasis) were performed. Any incongruous cases are flagged and investigated. Men who died with relapsed prostate cancer while on ADT, but in the absence of metastases, were coded according to their certified death cause.

The extracted data was imported into a Microsoft Access 2010 database for further processing, and then survival and other outcomes calculated using SPSS, v 18. (SPSS Inc). Parametric and nonparametric tests to determine significance between groups is used with actuarial (Kaplan−Meier) and multivariable (Cox regression) analysis. This project has received approval from our institutional ethics review board.

Results

Between the start of our brachytherapy program in 1998 and December, 2011, a total of 260 men with H-IR prostate cancer were treated with LDR brachytherapy. ADT was used in 121 (47%), for a median duration of 6 months, and was typically started 3 months before the implant, with an antiandrogen used only for flare protection for a few weeks. Patient characteristics are shown in Table 1.

Patients treated with ADT had longer follow-up, were more likely to have Grade Group 1 cancer, had more advanced T stage, and had greater percentage of their biopsy cores involved.

Biochemical control assessed by Phoenix nadir +2 or by threshold 0.4 did not significantly differ between those treated with ADT or not (Figs. 1 and 2 and Table 2). Multivariable analysis confirmed that ADT was not a significant factor for either definition of biochemical relapse; the only significant factors are Grade Group and baseline PSA (data not shown). For the threshold definition, the curves appear to diverge at times longer than the median follow-up suggesting that those not treated with ADT may have higher relapse rates with further follow-up. Exploration of PSA kinetics (Table 2) sheds further light on this; there were more men with a last follow-up PSA >0.2 who had not