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Long-term outcomes of prostate cancer patients with Gleason pattern 5 treated with combined brachytherapy and external beam radiotherapy

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ABSTRACT

PURPOSE: Recent reports have suggested relatively poor prognosis for prostate cancer patients with Gleason pattern 5 treated with dose-escalated external beam radiotherapy (XRT) and androgen deprivation therapy (ADT). We present the largest series of men with high-risk, Gleason pattern 5 prostate cancer treated with permanent interstitial brachytherapy and XRT.

METHODS AND MATERIALS: Between April 1995 and December 2008, 329 consecutive patients with National Comprehensive Cancer Network high-risk disease were treated with permanent interstitial brachytherapy. Most received XRT and ADT. Median followup was 7.2 years. The cause of death was determined for each deceased patient. Multiple clinical, treatment, and dosimetric parameters were evaluated for impact on the evaluated survival parameters.

RESULTS: At 10 years, biochemical progression-free survival, cause-specific survival (CSS), and overall survival for the group of high-risk patients as a whole was 91.1%, 95.5%, and 72.5%, respectively. There was no difference in biochemical progression-free survival between men with and without Gleason pattern 5 (89.7% vs. 91.8%; $p = 0.56$). However, men with Gleason pattern 5 had lower prostate cancer CSS (90.3% vs. 98.1%; $p = 0.011$). There was no difference in overall survival comparing men with and without Gleason pattern 5 disease (67.7% vs. 75.4%; $p = 0.14$).

CONCLUSIONS: Men with high-risk, Gleason pattern 5 histology treated with brachytherapy and XRT have excellent long-term outcomes, which compare favorably to dose-escalated XRT/ADT series without brachytherapy. Nonetheless, Gleason pattern 5 results in lower CSS than high-risk disease without Gleason pattern 5.

Keywords: High-risk prostate cancer; Gleason pattern 5; Brachytherapy; Outcomes

Introduction

The prognosis for men with clinically localized, high-risk prostate cancer treated with external beam radiotherapy (XRT) has improved significantly over the last 15 years. Most notably, the addition of androgen deprivation therapy (ADT) to standard dose XRT has been shown in several large, randomized studies to increase cause-specific survival (CSS) and overall survival (OS) (1–3). In addition, escalating external beam dose to 78–80 Gy without ADT has led to improvements in biochemical progression-free survival (bPFS) (4, 5). However, even with these improvements, disease recurrence for men with high-risk disease remains significant.

Recent publications have suggested that men with a Gleason 5 component have particularly poor outcomes (6), even in those receiving both ADT and dose-escalated XRT (7, 8). Because of this, it has been suggested that treatment intensification with systemic chemotherapy may be required to improve outcomes, particularly because of the high risk of systemic recurrence (6, 7). However, it is unclear whether adding systemic chemotherapy to dose-escalated XRT is the next logical step in treatment intensification.

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Adding a brachytherapy boost to XRT allows for delivery of significantly higher biologic effective dose than what can be achieved with XRT alone (9). This approach has yielded excellent medium- and long-term results for men with National Comprehensive Cancer Network (NCCN) high-risk disease (9–11). However, there are limited data regarding the benefit of brachytherapy in the subcategory of high-risk men with Gleason grade 5. The purpose of this study is to report outcomes of men with Gleason grade 5 treated with brachytherapy to help determine the efficacy of brachytherapy in this patient population.

Methods and materials

Between April 1995 and December 2008, 329 consecutive patients with NCCN high-risk prostate cancer were treated with permanent interstitial brachytherapy by a single brachytherapist (GSM). This included men with either prostate-specific antigen (PSA) level higher than 20 ng/mL, Gleason score of 8 or higher, or Stage T3a or higher. All biopsy slides were reviewed by a single pathologist (EA). Patients were clinically staged by medical history, physical examination including digital rectal examination, and serum PSA determination. Bone scans and CT of the abdomen and pelvis were obtained for patients with high-risk disease. Of the 329 men with high-risk disease, 119 had primary or secondary Gleason pattern 5. The remaining 210 men had high-risk disease without Gleason pattern 5.

Of these 329 men, 239 (72.7%) received ADT. A total of 190 men (57.8%) received ADT for more than 6 months, whereas 49 men (14.9%) received the therapy for 6 or fewer months. In patients receiving ADT, ADT was initiated 3 months before implantation and consisted of a luteinizing hormone–releasing agonist and an antiandrogen. The maximum duration of ADT was 36 months. Median duration of ADT was 8 months.

A total of 306 patients (93.0%) received supplemental XRT. In general, XRT consisted of 45–50.4 Gy delivered in 1.8 Gy fractions with 15–18 MV photons delivered via a multifield technique with custom treatment devices. For patients with 10% or lower risk of pelvic lymph node involvement (12), the target volume consisted of the prostate gland and seminal vesicles. For patients with higher than 10% risk of pelvic lymph node involvement, the pelvic lymph nodes were also included in the target volume. Supplemental XRT was delivered before implantation.

The brachytherapy planning treatment volume consisted of the entire prostate gland with a 5-mm periprostatic margin and the proximal 1.0 cm of the seminal vesicles (13). All postimplant dosimetric calculations were based on Day 0 evaluation of postimplant coverage of the planning treatment volume. ^{103}Pd was used in 316 patients (96.0%) and ^{125}I in 13 patients (4.0%). In general, the implant was used as a boost to XRT; and the minimum peripheral dose was 90 Gy for ^{103}Pd and 110 Gy for ^{125}I. For a small group of men for whom implant was used as monotherapy, ^{103}Pd was used exclusively and the minimum peripheral dose was 125 Gy.

Patients were monitored by physical examination including digital rectal examination and serum PSA determination at 3- and 6-month intervals. The endpoint of the analysis was CSS, bPFS, and OS. Cause of death was determined for each deceased patient. Patients with metastatic prostate cancer or castrate-resistant disease without obvious metastases who died of any other cause were classified as dead of prostate cancer. All other deaths were attributed to the immediate cause of death. The bPFS was defined as a PSA level of 0.40 ng/mL or lower after nadir, which has been shown to be a particularly sensitive definition for identifying patients who have failed treatment (14). Patients who failed to nadir below 0.40 ng/mL were categorized as a biochemical failure. Multiple clinical, treatment, and dosimetric parameters were evaluated for impact on survival.

Clinical and treatment variables that were continuous were compared using an independent t test. Categorical variables were compared using a χ^2 analysis.

Univariate and multivariate predictors of OS were determined using a Cox regression analysis. A competing risks analysis was used to determine univariate and multivariate predictors of biochemical failure and cause-specific mortality. Cumulative incidence using a competing risk regression technique was also used to present differences between the two groups for biochemical failure and cause-specific mortality. Overall mortality was presented graphically using Kaplan–Meier curves. All analyses were performed using Stata version 12.0 (StataCorp LP, College Station, TX). Significance was set at p-value of 0.05 or lower.

Results

Table 1 summarizes the clinical and treatment characteristics of men included in the analysis. Of the 329 men with high-risk disease, 210 men had maximum Gleason pattern 4 on biopsy, whereas 119 men had a Gleason pattern 5 component. Median length of followup was 7.2 years. The median Day 0 D_{90} for all patients was 121.2% of the prescription implant dose. Most men received ADT, although ADT was used more commonly and for longer duration in men with Gleason pattern 5 ($p < 0.001$). Almost all men in the cohort received supplemental XRT.

At 10 years, bPFS (PSA nadir $\leq$ 0.40 ng/mL), bPFS (PSA nadir + 2), CSS, and OS for the group of high-risk patients as a whole was 91.1%, 90.9%, 95.5%, and 72.5%, respectively (Fig. 1). When stratified based on presence or absence of Gleason pattern 5, there was no difference in bPFS between men with and without Gleason pattern 5 (89.7% vs. 91.8%; $p = 0.56$; Fig. 2A). However, despite similar biochemical recurrence rates, men with