ELSEVIER

Brachytherapy ■ (2016) ■

BRACHYTHERAPY

High−dose rate brachytherapy monotherapy without androgen deprivation therapy for intermediate-risk prostate cancer

Shyamal Patel[1,2,*], D. Jeffrey Demanes[1], Omar Ragab[1], Mingle Zhang[1], Darlene Veruttipong[1], Kristine Nguyen[1], Sang-June Park[1], Leonard Marks[3], Allan Pantuck[3], Michael Steinberg[1], Mitchell Kamrava[1]

[1]*Department of Radiation Oncology, University of California, Los Angeles, Los Angeles, CA*
[2]*Department of Radiation Oncology, University of Arizona Cancer Center at Dignity Health St. Joseph's Hospital and Medical Center, Phoenix, AZ*
[3]*Department of Urology, University of California, Los Angeles, Los Angeles, CA*

ABSTRACT

PURPOSE: Outcomes using high-dose-rate (HDR) brachytherapy monotherapy (without androgen deprivation therapy or external beam radiation therapy) for National Comprehensive Cancer Network−defined intermediate-risk (IR) patients are limited. We report our long-term data using HDR monotherapy for this patient population.

METHODS AND MATERIALS: One-hundred ninety IR prostate cancer patients were treated 1996−2013 with HDR monotherapy. Biochemical prostate-specific antigen (PSA) failure was per the Phoenix definition. Acute and late genitourinary and gastrointestinal toxicities were graded according to Common Toxicity Criteria of Adverse Events, version 4. Kaplan−Meier (KM) biochemical progression-free survival (BPFS), cause-specific survival, and overall survival rates were calculated. Univariate analyses were performed to determine relationships with BPFS. The median patient age was 66 years (43−90), and the median initial PSA was 7.4 ng/mL. The Gleason score was ≤6 in 26%, 3 + 4 in 62%, and 4 + 3 in 12%. The median treatment $BED_{1.5}$ was 254 Gy; 83% of patients were treated with a dose of 7.25 Gy × six fractions delivered in two separate implants.

RESULTS: With a median follow-up of 6.2 years, KM BPFS at 5/8 years was 97%/90%, cause-specific survival at 8 years was 100%, and overall survival at 5/8 years was 93%/88%. Late genitourinary toxicities were 36.3% Grade 1, 18.9% Grade 2, and 3.7% Grade 3. Late gastrointestinal toxicities were 6.3% Grade 1, 1.1% Grade 2, and no Grade ≥3. Of the patients with no sexual dysfunction before treatment, 68% maintained potency. Age, initial PSA, T stage, Gleason score, prostate volume, and percent positive cores did not correlate with BPFS. Stratifying by favorable vs. unfavorable IR groups did not affect BPFS.

CONCLUSIONS: HDR brachytherapy monotherapy represents a safe and highly effective treatment for IR prostate cancer patients with long-term follow-up.

Keywords: Prostate brachytherapy; HDR brachytherapy monotherapy; High-dose-rate brachytherapy for prostate cancer; Intermediate-risk prostate cancer; Intermediate prostate cancer without androgen deprivation therapy; Brachytherapy without external beam radiation therapy

Introduction

The National Comprehensive Cancer Network provides guidance for stratifying prostate cancer patients into five risk groups that have varying clinical outcomes after definitive treatment. Although being able to place patients into these risk groups is helpful, it is also apparent that patients within the same risk group have heterogeneous clinical outcomes. This is particularly true, for example, for intermediate-risk (IR) patients. In an effort to improve the IR stratification, Zumsteg *et al.* (1) proposed grouping patients into "favorable" and "unfavorable" groups with 8-year prostate-specific antigen (PSA) biochemical failure (BF) rates of about 14% vs. 29% for "favorable" vs. "unfavorable" patients. The majority of patients in this study were treated with modern external beam radiation

Received 21 September 2016; received in revised form 22 October 2016; accepted 7 November 2016.

The authors have no actual or potential conflicts of interest to disclose.

* Corresponding author. Department of Radiation Oncology, University of California, Los Angeles, 200 Medical Plaza, Suite B265, Los Angeles, CA 90095. Tel.: +1-310-206-2510; fax: +1-310-794-9795.

E-mail address: patels2010@gmail.com (S. Patel).

1538-4721/$ - see front matter
http://dx.doi.org/10.1016/j.brachy.2016.11.002

therapy (EBRT) regimens, and the prognostic significance of this stratification remains uncertain when delivering even higher doses of radiation with brachytherapy (BT). Merrick *et al.* (2), for instance, found 15-year BF rates after low-dose-rate (LDR) BT for favorable vs. unfavorable IR patients to be 2.2% vs. 7.1%. So while there was still an increased risk of BF between the groups, the magnitude of difference is much smaller than that seen after EBRT.

Although there are more long-term outcome reports with LDR BT, HDR BT has substantial efficacy and toxicity data. It makes therapeutic use of the low alpha/beta ratio of prostate cancer and has the flexibility to ensure proper target coverage with highly reproducible dosimetry (3). Excellent long-term results have been reported for HDR BT in combination with EBRT across all risk groups (4, 5). There is more limited long-term data using HDR monotherapy (without EBRT) and the data that does exist are predominantly in low-risk patients (6, 7). Given the unclear role of treating the pelvic lymph nodes (8) and the uncertain benefit of androgen deprivation therapy (ADT) (9) when delivering high-dose radiation therapy, our group regularly uses HDR monotherapy (without EBRT or ADT) in the treatment of IR patients. The purpose of this work, which represents the largest and longest reported experience of HDR BT monotherapy without ADT for IR patients, is to share our long-term efficacy and toxicity outcomes and identify prognostic factors that may guide management decisions.

Methods and materials

In this institutional review board−approved study, 190 consecutive patients with IR prostate cancer (*American Joint Committee on Cancer Seventh Edition* ≤ clinical T2c and PSA 10−19.9 ng/mL or Gleason score 7) were treated with HDR interstitial BT monotherapy between 1996 and 2013 and included in a prospectively collected registry. Patients who received EBRT or ADT (neoadjuvantly, concurrently, or adjuvantly) were excluded. Patients with recurrent prostate cancer and those who underwent partial gland treatment were also excluded.

Our HDR BT method has previously been reported (10). Briefly, we implant interstitial catheters in a predefined distribution with transrectal ultrasound guidance. Catheters are first inserted at the periphery of the prostate in an anterior-to-posterior manner followed by insertion of the intraprostatic catheters. At the conclusion of the procedure, a CT scan is performed and then used for delineation of the organs at risk and the clinical target volume. Our clinical target volume includes the prostate and the proximal seminal vesicles. CT-based treatment planning is performed and our dosimetric criteria include the following: $D_{90} > 100\%$, $V_{100} > 97\%$, $V_{150} < 35\%$, rectal $D_{0.1cc}$ <85%, bladder $D_{0.1cc}$ 80−95%, and urethra $D_{0.1cc} < 110\%$.

Patient disease characteristics and treatment parameters were collected. Outcome data including PSA BF, cause-specific survival (CSS), and overall survival (OS) and acute and late toxicities were collected. BF was scored per the Phoenix definition of nadir +2. Untreated PSA bounces, where the PSA increased >2 ng/mL but then decreased without intervention to less than nadir +2, were not considered to represent BF (11). Acute and late (>6 months post-treatment) genitourinary (GU) and gastrointestinal (GI) toxicities were graded according to the Common Toxicity Criteria of Adverse Events (CTCAE), version 4. Sexual function was also collected and scored per CTCAE v4.0 before treatment and on each follow-up visit after treatment. To calculate the biologically effective dose (BED), an alpha/beta ratio of 1.5 was assumed (12).

For statistical analysis, we used SAS, version 9.4 (SAS Institute, Cary, NC) with a level of statistical significance set at $p = 0.05$. Kaplan−Meier (KM) biochemical progression-free survival (BPFS), CSS, and OS rates were calculated. Patients were also stratified by Gleason score and by favorable vs. unfavorable risk (≥50% positive cores, Gleason 4 + 3, or ≥2 IR factors) (1) for further KM analysis. Univariate regression analyses via the Cox proportional hazards model were used to determine relationships with BPFS. Logistic regression was performed to assess the impact of previous transurethral resection of the prostate (TURP) on toxicity.

Patient and treatment characteristics

Patient characteristics and treatment parameters are listed in Table 1. Of the 190 patients in this study, 143 were treated at California Endocurietherapy (CET) in Oakland, CA, and 47 at the University of California, Los Angeles (UCLA) (CET moved to UCLA in 2010). Per the criteria delineated by Zumsteg *et al.* (1), 62% were classified as favorable IR, whereas 38% were classified as unfavorable. The median $BED_{1.5}$ was 254 Gy with a range of 206−279 Gy; 83% of patients were treated with 7.25 Gy × six fractions in 2 separate implants spaced 1 week apart.

Results

Oncologic outcomes

At a median follow-up of 6.2 years (range, 0.3−14.5), 9 of 190 patients (4.7%) experienced a BF. Kaplan−Meier BPFS was 97% and 90% at 5 and 8 years, respectively, and is shown in Fig. 1. The median PSA nadir was 0.10 ng/mL (range, 0.002−2.89) and time to nadir was 2.82 years (range, 0.06−11.0).

The median time to BF was 6.2 years (range, 0.68−9.4). Of the nine failures, one was local (biopsy proven), one was regional nodal (biopsy proven), and one was distant (bone metastasis to the spine). Six patients were initiated on salvage ADT for a rising PSA with no imaging evidence of recurrent disease. These 6 patients declined repeat prostate biopsy to evaluate for local disease recurrence. Table 2