Treatment of intermediate-risk prostate cancer with Cs-131: Long-term results from a single institution

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ABSTRACT

Purpose: To evaluate our institutional outcomes utilizing Cs-131 prostate brachytherapy (PB) for the intermediate-risk (IR) group of prostate cancer patients.

Methods and materials: We reviewed a prospectively collected database of men treated with Cs-131 PB between 2006 and 2019. Patients with less than 24-months follow-up were excluded. Patients were classified as IR if they had one of the following factors: Gleason Score 7, prostate specific antigen >10 but <20 ng/mL, or T2b-c on clinical exam. We defined unfavorable-IR (UIR) as having either Grade Group 3, >1 IR factors, or ≥50% positive core biopsies. The Kaplan-Meier method was used to estimate actuarial event-time probabilities for biochemical freedom from disease (BFD).

Results: A total of 335 patients with a median follow-up of 70.1 months (IQR 48.3–106.3 months) were identified. Androgen deprivation therapy (ADT) was used in 7.2% of patients. Favorable-IR (FIR) patients were commonly treated with PB alone (91.8%). FIR patients who underwent PB alone had a 5-year BFD of 98.1%. UIR patients were commonly treated with external beam radiotherapy plus PB (61.2%). These patients had 5-year BFD of 91.1%. The 5-year BFD for UIR patients treated without ADT was 90.9%, whereas it was 95.0% among UIR patients treated with ADT (log-rank p = 0.83).

Conclusions: FIR patients have excellent outcomes when treated with PB alone. External beam radiotherapy plus PB is a reasonable treatment approach for UIR patients. Future studies may elucidate which IR patients would benefit from treatment intensification. © 2021 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords: Cs-131; Prostate cancer; Brachytherapy; Intermediate-risk

Introduction

Intermediate-risk (IR) prostate cancer is an extremely heterogeneous risk group. Three IR factors (Gleason Score 7, prostate specific antigen (PSA) 10–19.9 ng/mL, and clinical stage T2b-c) are widely accepted (1). Efforts have been made to separate patients into favorable-IR (FIR) and unfavorable-IR (UIR), though there is some debate as to the exact prognostic factors that should be used to define these (2,3). The National Comprehensive Cancer Network (NCCN) defines UIR as having two or more IR factors, Grade Group (GG) 3 histology, or ≥50% biopsy cores positive (4). However, the percent of biopsy core involvement has not been adopted widely (5).

Prostate brachytherapy (PB) has accrued a significant amount of data for its use in treating IR prostate cancer, either as single modality or part of a multimodality treatment regimen (6). How, when, and if PB is used for any single patient with IR prostate cancer often remains at the physician’s discretion, with recommendations for treatment of IR patients ranging from single modality (or active surveillance) to trimodality therapy.

Cesium-131 (Cs-131) is a newer isotope used for PB. The major benefit of Cs-131 is the shorter duration of the bothersome voiding symptoms that accompany PB (7–9).
For this reason, our center began using this isotope exclusively in our PB program in 2006 (10). Results using Cs-131 have been excellent and similar across different institutions (11–13). Here, we present our data with long term follow up of using Cs-131 PB in the treatment of IR prostate cancer. This should provide guidance to the treatment of patients with IR prostate cancer undergoing PB.

**Methods and materials**

All patients with IR prostate cancer who underwent PB with Cs-131 at our institution and had at least 24 months of follow up after PB were included in the present study. IR was defined as having a Gleason Score 7, PSA 10–19.9 ng/mL, or clinical stage T2b-c. Patients were further stratified into FIR and UIR categories using the NCCN criteria (4). Patients were designated as having FIR if they had only one of the intermediate risk factors (n = 147, 43.9%). Patients were designated as having UIR (n = 188, 56.1%) if they had greater than one intermediate risk factor, GG 3 histology, or ≥50% positive core biopsies. Patients were characterized as having received monotherapy if they underwent PB alone. Combined radiotherapy consisted of external beam radiotherapy (EBRT) followed by PB approximately 4 weeks after patients completed their EBRT. Patients undergoing EBRT (n = 150, 44.8%) received 45 Gy in 25 fractions to the prostate and seminal vesicles. Most (90.7%) did not have their pelvic nodes treated. The majority of patients who underwent EBRT (92.7%) were treated with intensity modulated radiotherapy. Patients undergoing trimodal therapy received combined radiotherapy plus androgen deprivation therapy (ADT). In general, patients with FIR were treated with PB as monotherapy and patients with UIR were treated with combined radiotherapy. Patient preference or starting the treatment regimen prior to our center being involved with the care occasionally led to deviation from these recommendations. The technique of implantation at our center has been previously described (10).

Patients undergoing PB as monotherapy were treated with a prescribed dose of 115 Gy, while patients undergoing combined modality were treated with a prescribed dose of 85 Gy. Targets for dosimetry were: D90 >110%, V100 >90%, V150 <50%, and V200 <20%. CT-based dosimetry was obtained on the day of PB (day 0). Patients were asked to obtain a serum PSA every 3 months for the first year after the procedure, every 6 months until year five, and then annually.

Patients who died for reasons other than prostate cancer prior to 24 months after their procedure and had not failed were not included in the analysis. The Phoenix definition (absolute nadir plus 2 ng/mL dated at the event) was used to define biochemical freedom from disease (BFD) (14).
Statistical analysis was conducted using IBM SPSS statistical software version 25 (IBM, Armonk, NY). The Kaplan Meier method was used to estimate BFD, which was calculated from time of implant to the date of last available PSA. The log-rank test was used to compare BFD between groups. Univariate analysis (UVA) using Cox regression was performed to identify predictors of BFD. All p values were 2-sided with a threshold for significance set at $p < 0.05$.

### Results

A total of 335 patients with IR prostate cancer who underwent CS-131 PB were included in this study. Clinical characteristics of the cohort appear in Table 1. Patients were classified as UIR (n = 188) due to GG3 (n = 104), >1 IR factor (n = 44), and ≥50% cores positive (n = 40). The median follow-up was 70.1 months (interquartile range [IQR] 48.3–106.3 months).

We treated 147 FIR patients. The majority of these (n = 135) were treated with PB alone. Their outcome is shown in Fig. 1. The 5-year BFD for FIR patients treated with PB alone was 98.1% (95% confidence interval [CI] 95.4–100).

As noted above, some FIR patients were treated with combined radiotherapy (n = 11) or even trimodal therapy (n = 1). The 5-year BFD for patients treated with combined modality was 91.7% (95% CI 76.0–100.0).

Most men with UIR were treated with combined radiotherapy (n = 115). Their outcome is shown in Fig. 2. The 5-year BFD for UIR patients treated with combined radiotherapy was 91.1% (95% CI 85.2–97.0%). Again, some of these patients were treated with PB alone (n = 50) or trimodal therapy (n = 23). The 5-year BFD of UIR patients treated with these regimens were 90.2% (95% CI 81.0–99.4) and 95.0 (95% CI 85.4–100.0), respectively. The numbers are small, but there was no difference in BFD between treatment modality (log-rank $p = 0.96$). In total, UIR patients treated without ADT (n = 165) had a 5-year BFD of 90.9% (95% CI 85.8–96.0).

A total of 40 patients were considered UIR if having ≥50% positive cores was factored in, who would be considered FIR without factoring in core positivity. 17 of these patients were treated with PB alone, 21 of these patients were treated with combined radiotherapy, and two were treated with trimodal therapy. At 5-years, none of these patients had a biochemical failure.
A total of 24 patients were treated with ADT as part of their regimen (one FIR and 23 UIR). Their 5-year BFD was 95.0% (85.4–100). The characteristics of UIR patients treated with trimodal therapy is shown in Supplemental Table 1. UIR patients with ≥2 IR factors were more likely to receive ADT (n = 14; 60.9%) compared to patients with one IR factor (n = 59; 35.8%) (p = 0.02). Numbers became too small to draw conclusions about BFD in different subgroups, though of interest, the 5-year BFD of the 5 patients who had all three IR factors was 40%.

There was no statistical difference in outcome between FIR and UIR patients, as the 5-year BFD was 97.6% (95% CI 94.9–100.0) and 91.4% (95% CI 86.9–95.9), respectively (log-rank p = 0.11). This is likely due to aggressiveness of treatment, as UIR were more likely to be treated with combined modality (73.4%; p < 0.01). In our cohort, 243 men were disease free with at least 48-months of follow up. The median PSA for these 243 patients at 48-months was 0.06 ng/mL (IQR 0–0.13), with most patients having a PSA of ≤0.2 ng/mL (59.7%).

In the total cohort, among patients with biochemical failures, 11 out of 26 (42.3%) happened within the first 48-months after PB. For the 15 patients who experienced biochemical failure after 48-months, the PSA at the 48-months timepoint were as follows: 4 patients had a PSA of ≤0.2 ng/mL, six had a PSA of 0.5–1.0 ng/mL, four had a PSA >1.0 ng/mL, and one had an unknown PSA value. Table 2 outlines predictors of BFD. On UVA, age and PSA level at diagnosis were identified as significant predictors of BFD. Multivariate analysis was not performed due to the limited number of events.

**Discussion**

IR prostate cancer is an extremely heterogeneous disease (1). There are generally accepted risk factors and generally accepted definitions of FIR and UIR (4,5). Core positivity has also been postulated as a risk factor, though with less robust data (4). There are also generalized treatment recommendations, though the variance in how IR patients are treated is wide, especially given the ever-changing landscape of definitions and incoming data (15). Also, clinically localized prostate cancer is a slow-growing malignancy that requires long-term follow-up to determine the success of any oncologic intervention. This makes the adoption of new definitions and new interventions diffi-
Table 2  
Predictors for biochemical failure in intermediate-risk patients  

<table>
<thead>
<tr>
<th>Predictors on univariate analysis</th>
<th>No (n = 309)</th>
<th>Yes (n = 26)</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gleason Grade Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>1</td>
<td>21 (91.3%)</td>
<td>2 (8.7%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>196 (94.2%)</td>
<td>12 (5.8%)</td>
<td>0.67</td>
<td>0.15–3.00</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>92 (88.5%)</td>
<td>12 (11.5%)</td>
<td>1.59</td>
<td>0.35–7.12</td>
<td></td>
</tr>
<tr>
<td><strong>IR Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>Favorable</td>
<td>139 (94.6%)</td>
<td>8 (5.4%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfavorable</td>
<td>170 (90.4%)</td>
<td>18 (9.6%)</td>
<td>1.97</td>
<td>0.85–4.53</td>
<td></td>
</tr>
<tr>
<td><strong>ADT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.86</td>
</tr>
<tr>
<td>No</td>
<td>287 (92.3%)</td>
<td>24 (7.7%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22 (91.7%)</td>
<td>2 (8.3%)</td>
<td>1.14</td>
<td>0.27–4.85</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>≤65</td>
<td>118 (87.4%)</td>
<td>17 (12.6%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>191 (95.5%)</td>
<td>9 (4.5%)</td>
<td>0.37</td>
<td>0.16–0.83</td>
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<tr>
<td><strong>Clinical T stage</strong></td>
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<td></td>
<td>0.63</td>
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<tr>
<td>T1</td>
<td>221 (91.4%)</td>
<td>21 (8.6%)</td>
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<td></td>
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<tr>
<td>T2a</td>
<td>53 (96.4%)</td>
<td>2 (3.6%)</td>
<td>0.49</td>
<td>0.12–2.10</td>
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<tr>
<td>T2b</td>
<td>33 (91.7%)</td>
<td>3 (8.3%)</td>
<td>0.87</td>
<td>0.26–2.93</td>
<td></td>
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<tr>
<td><strong>PSA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>&lt;10</td>
<td>251 (93.7%)</td>
<td>17 (6.3%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10–20</td>
<td>56 (86.2%)</td>
<td>9 (13.8%)</td>
<td>2.88</td>
<td>1.27–6.53</td>
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<tr>
<td><strong>NCCN IR Factors</strong></td>
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<td></td>
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</tr>
<tr>
<td>1</td>
<td>243 (92.7%)</td>
<td>19 (7.3%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>66 (90.4%)</td>
<td>7 (9.6%)</td>
<td>1.58</td>
<td>0.66–3.80</td>
<td></td>
</tr>
<tr>
<td><strong>Cores positive (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>&lt;50</td>
<td>232 (93.2%)</td>
<td>17 (6.8%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>76 (90.5%)</td>
<td>8 (9.5%)</td>
<td>1.28</td>
<td>0.55–2.97</td>
<td></td>
</tr>
</tbody>
</table>

HR = Hazard Ratio; CI = Confidence Interval; IR = Intermediate-Risk; ADT = Androgen Deprivation Therapy; PSA = Prostate Specific Antigen; NCCN = National Comprehensive Cancer Network.

cult. More data is always beneficial in supporting recommended changes, especially with IR prostate cancer patients treated with Cs-131 PB, in which little data exists; and none with our reported detailed treatment regimens and with this length of follow-up.

We now have over 14 years of experience with Cs-131 prostate implants and continue to publish our biochemical outcomes to build the body of literature to support the continued use of this isotope. The primary benefit of Cs-131 PB is the shorter duration of the urinary morbidity associated with prostate brachytherapy (7–9). The present study was undertaken to report long-term PSA outcomes in patients with IR prostate cancer treated with Cs-131 PB at our institution with the hope that specific treatment recommendations can be made based on the data.

Our data concludes that patients with FIR prostate cancer can be treated with Cs-131 PB as monotherapy, as our patients in this cohort had a BFD of 98.1%. This allows these patients to be treated without supplemental EBRT and/or ADT, both of which can serve to add toxicity (6).

There is data to treat UIR patients with trimodal therapy (16). The prospective randomized ASCENDE-RT trial included UIR patients but mostly included high-risk patients, so whether trimodal therapy is needed in UIR patients is debated. We treated most of our UIR patients with combined radiotherapy and the vast majority (87.8%) without ADT. The 5-year BFD for UIR patients treated without ADT was 90.9%, whereas the 5-year BFD among UIR patients treated with ADT was 95.0% (log-rank p = 0.83). Hence, the absolute value of ADT within our cohort is low. There may still be an advantage of ADT and determining this as well as identifying characteristics of patients within this group who benefit from trimodal therapy should be the focus of future studies. Perhaps this can be clinical characteristics (patients in our cohort with all the three IR factors did poorly), or genomic markers (15). Based on our data, if the wish is to avoid ADT due to treatment-related toxicities, it is reasonable to treat UIR patients with combined radiotherapy.

Our results compare favorably with previously published data. Moran et al. found a 5-year biochemical control rate for both FIR and UIR of 98.8% (12). However, the specifics (supplemental EBRT, ADT, etc.) of how these patients were treated with respect to their risk grouping was not reported. Also, the number of biopsy cores positive was not reported. Tom et al. published a similar study using data from patients treated with I-125 monotherapy (17). They found a significant difference in biochemical control between FIR and UIR. The 5-year BFD was 95.7% and 83.0% for FIR and UIR, respectively. Their conclusion was
that FIR do well with PB as monotherapy, whereas alternative treatment intensification strategies should be utilized for UIR. Since implementation of our PB program, we have treated the majority of FIR patients with Cs-131 PB alone and UIR with combined radiotherapy. No difference in BFD was found between groups, probably due to radiation treatment intensification among UIR patients.

Core positivity has been postulated as an additional risk factor (4); however, some consensus guidelines do not take this factor into account (5). Within our cohort, 40 patients were reclassified from FIR into UIR due to core positivity. Although the numbers are fairly small, patients considered UIR based solely on core positivity did well, even with PB alone. Also, core positivity was not found to be a predictor of biochemical failure (Table 2). It would be presumptuous to completely rule out core positivity as an independent risk factor, though based on our data, it certainly seems to be less predictive than the classic intermediate risk factors.

Limitations of this study include its retrospective design. Also, we did not include patients who underwent external beam radiotherapy plus ADT. A recent meta-analysis suggests that ADT conveys an overall survival benefit for all IR patients, whereas an advantage was not seen for patients undergoing combined radiotherapy (18). Hence, future analysis could be performed to compare all treatment modalities, especially among UIR patients.

Conclusions

IR prostate cancer can be treated with Cs-131 PB with excellent results. Our recommendation is to treat FIR patients with PB as monotherapy and to treat UIR patients with combined radiotherapy. Although a small number of patients in our cohort received ADT, the vast majority of patients treated without ADT did well. Future studies may elucidate which patients benefit from the addition of ADT. Though core positivity will continue to be considered, treatment decisions should not be based strictly on percent of cores positive.

Declaration

The data were presented as a poster presentation at ASTRO 2020 annual meeting.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.brachy.2021.08.008.

References


