Cesium 131 versus iodine 125 implants for prostate cancer: evaluation of early PSA response

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Introduction: *Given the shorter half-life of cesium-131 (Cs-131) compared to iodine-125 (I-125), we hypothesized that initial PSA outcomes may differ. We compare initial PSA outcomes in men undergoing Cs-131 prostate brachytherapy to men treated with I-125.*

Patients and methods: *The first post-treatment PSA (obtained 3-6 months after the procedure) was compared in patients undergoing I-125 prostate brachytherapy to that of patients undergoing Cs-131 prostate brachytherapy at the same institution. Comparisons included the total cohort as well as low and intermediate risk patients.*

Results: *Mean pre-treatment PSA was 6.9 ng/mL in the I-125 cohort, and 6.9 ng/mL in the Cs-131 cohort. Mean initial post-treatment PSA was 0.9 ng/mL (range < 0.1-4.6) in the I-125 cohort and 1.2 ng/mL (range < 0.1-23.5) in the Cs-131 patients. For low risk patients, mean pre-treatment PSA was 5.8 ng/mL in the I-125 cohort, and 5.1 ng/mL in the Cs-131 cohort. Initial mean post-treatment PSA for low risk patients was 1.2 ng/mL (range < 0.1-4.6) in the I-125 group and 1.0 ng/mL (range < 0.1-2.9) in the Cs-131 patients (p = 0.37). For intermediate risk patients, mean pre-treatment PSA was 7.3 ng/mL in the I-125 cohort, and 7.3 ng/mL in the Cs-131 cohort. Mean initial post-treatment PSA in intermediate risk patients was 1.5 ng/mL (range < 0.1-2.9) in the I-125 group and 1.2 ng/mL (range < 0.1-4.6) in the Cs-131 patients (p = 0.52).*

Conclusions: *Given the shorter half-life of Cs-131 compared to I-125, we hypothesized that initial post-brachytherapy PSA levels were similar between men receiving treatment with Cs-131 and I-125. The aim of the present study is not to predict long term outcome after Cs-131 prostate brachytherapy, but rather to simply compare initial PSA outcomes in men undergoing prostate brachytherapy with I-125 to Cs-131. Long term data are needed to document cancer control achieved with Cs-131.*

Key Words: prostate adenocarcinoma, PSA, prostate brachytherapy, cesium

Introduction

Prostate brachytherapy is now an accepted treatment option for clinically localized prostate cancer. Prostate brachytherapy (PB) represents a minimally invasive treatment option associated with low morbidity[1] and a quick return to full activity after the procedure. Five and 10-year biochemical disease-free survival rates after PB are comparable to radical prostatectomy (RP) and three-dimensional conformal external-beam radiation therapy (EBRT).[2,3]

Cesium-131 (Cs-131), a novel isotope developed for prostate brachytherapy (IsoRay Medical, Richland, WA, USA), is an alternative to palladium-103 (Pd-103) and iodine-125 (I-125).[4,5] A shorter duration of bothersome voiding symptoms associated with prostate brachytherapy is an important potential advantage of Cs-131. The decreased duration of

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urinary morbidity may be due to the short half-life of Cs-131 (9.7 days, versus 60 days with I-125). The shorter half-life of Cs-131 may allow for a quicker resolution of the bothersome lower urinary tract symptoms that accompany PB.

Although clinical trials have defined Cs-131 dosing regimens,[6-9] there have been few reports to date on PSA outcomes after PB. The effect of the shorter half-life of Cs-131 on initial PSA outcomes has not been thoroughly evaluated. The present study reports initial PSA outcomes following Cs-131 and compares these results with the initial PSA outcomes in patients undergoing I-125 PB. Initial post-brachytherapy PSA levels may predict PSA spike[10] and disease free survival at 48 months following implantation,[11] and serve as an independent predictor of local relapse-free survival.[12]

By comparing initial PSA outcomes in Cs-131 with initial PSA outcomes in our I-125 PB patients, we hope to provide practitioners of prostate brachytherapy who have experience with I-125 brachytherapy information as to what to expect in terms of initial PSA outcomes in men undergoing PB with Cs-131. The aim of the present study is not to predict long term outcome after Cs-131 prostate brachytherapy, but rather to simply compare initial PSA outcomes in men undergoing prostate brachytherapy with I-125 to Cs-131. Long term cancer control is not addressed in this study.

Methods

We retrospectively compared initial PSA outcomes in the first 100 patients undergoing I-125 prostate brachytherapy with the first 100 patients undergoing Cs-131 prostate brachytherapy at our institution. Longitudinal databases have been created to prospectively follow all patients undergoing prostate brachytherapy at our institution. Our prostate brachytherapy program began in 2001, and began using Cs-131 in September 2006 hoping to realize the shorter duration of urinary morbidity that may be associated with the use of this isotope.

Patients were stratified by the D'Amico classification system[13] into low risk (PSA ≤ 10 ng/mL and Gleason ≤ 6), intermediate risk (PSA > 10 ng/mL or Gleason 7), and high risk (PSA > 20 ng/mL or Gleason 8-10) groups for further analysis. Patients were requested to undergo PSA testing every 3 months for the first year, every 6 months in years two through five, and annually thereafter. The small number of patients in the high risk cohort precluded statistical comparisons in these men. The prescribed doses for patients implanted with Cs-131 or I-125 as monotherapy were 115 Gy and 145 Gy, respectively. CT-based dosimetry was obtained 1 month after the procedure in the I-125 patients, and the day of the procedure in the Cs-131 patients. Calculation of dosimetry was performed on different days for different isotopes in an attempt to account for the significant effect of post-implant edema on the dosimetry of Cs-131, which has a very short half-life. The D90 (minimum dose received by 90% of the prostate) and V100 (volume of prostate receiving at least 100% of the prescribed dose) were compared between the two cohorts.

Mean pre- and post-treatment PSA levels were compared with the Student t-test and the correlations were compared by chi-square test. Since patients treated with neo-adjuvant androgen deprivation therapy (ADT) are likely to have an undetectable initial PSA, patients who received ADT were excluded from the analysis. In our initial prostate brachytherapy experience, patients treated with combination therapy (external beam radiotherapy plus prostate brachytherapy) received Pd-103 rather than I-125, therefore we could not compare I-125 and Cs-131 in patients undergoing combination therapy as no patients in our I-125 cohort received combination therapy.

Results

Patient demographics and tumor characteristics are reported in Table 1. The median patient age was 69 years (range 45-79) years in the I-125 cohort and 65 years (range 50-79) in the Cs-131 cohort. The distribution of

TABLE 1. **Patient demographics and tumor characteristics**

	I-125	**Cs-131**	**p value**
Age (yrs)			
Median	69	65	0.031
Range	45-79	50-79	
Mean pretreatment PSA (ng/mL)	6.9 ± 5.4	6.9 ± 7.6	0.95
Gleason score			
≤ 6	87	48	
7	12	45	
8-9	1	7	
# Clinical stage (%)			
T1c	80 (80)	84 (84)	
T2a	17 (17)	8 (8)	
T2b	2 (2)	6 (6)	
T2c	1 (1)	2 (2)	
Prostate volume (cm^3)			
Median	40	40	0.34
Range	18-83	20-85	

TABLE 2. **Median seed number, total activity, and prostate dosimetry**

	^{125}I	^{131}Cs
Median seed # (range)	105 (49-120)	89 (50-145)
Median total activity (units)	39 (15-108)	170 (90-301)
Mean ± SD V_{100}	96% ± 3.9%	96% ± 3.8%
Mean ± SD D_{90}	122% ± 21%	113% ± 23%

Cs-131 = cesium-131; I-125 = iodine-125
SD = standard deviation
V_{100} = volume of prostate receiving at least 100% of prescribed dose
D_{90} = dose received by 90% of the prostate (recorded as % of prescribed dose)

low, intermediate, and high risk group patients was 45%, 46%, and 9%, respectively, in the Cs-131 group, and 87%, 13%, and 1%, respectively, in the I-125 cohort. The median number of seeds used and total activity were 89 (range 50-145) and 170 IU (range 90-301), respectively, for the Cs-131 patients; and 105 (range 49-120) and 39 mCi (range 15-108) in the I-125 patients, Table 2. Mean V100 was 96% ± 3.8% in the Cs-131 cohort and 96% ± 3.9% in the I-125 patients, while mean D90 was 113% ± 23% in the Cs-131 cohort and 122% ± 21% in the I-125 patients. PSA measurements following treatment were obtained at a mean of 4.1 months (range 3-6) and 4.9 months (range 3-6) in the I-125 and Cs-131 patients, respectively.

Mean pre-treatment PSA was 6.9 ng/mL (range 0.8-52) in the I-125 cohort, and 6.9 ng/mL (range 1.1-78) in the Cs-131 cohort, Table 3. Mean initial PSA obtained after treatment was 1.3 ng/mL (range < 0.1-4.6) in the I-125 group and 1.2 ng/mL (range < 0.1-23.5) in the Cs-131 patients. For low risk patients, mean pre-treatment PSA was 5.8 ng/mL (range 0.8-9.1) in the I-125 cohort, and 5.1 ng/mL (range 1.1-5.3) in the Cs-131 cohort (p = 0.06). Initial mean PSA after the procedure for low risk patients was 1.2 ng/mL (< 0.1-4.6) in the I-125 group and 1.0 ng/mL (< 0.1-2.9) in the Cs-131 patients (p = 0.37). Mean pre-treatment PSA was 7.3 ng/mL (range 2.6-14) in the I-125 intermediate risk cohort, and 7.3 ng/mL (range 1.7-15.3) in the intermediate risk Cs-131 cohort (p = 0.98). Mean initial PSA after the procedure in intermediate risk patients was 1.5 ng/mL (< 0.1-2.9) in the I-125 group and 1.2 ng/mL (< 0.1-4.6) in the Cs-131 patients (p = 0.52). No significant difference was found in the mean change between pre and post-treatment PSA in the I-125 and CS-131 patients when stratified by low and intermediate risk patients. There was no statistically significant difference in initial post-treatment PSA levels between patients undergoing prostate brachytherapy with Cs-131 and I-125 for any of the treatment groups.

Discussion

Ultrasound-guided transperineal prostate implant brachytherapy is an accepted treatment modality for clinically localized prostate cancer,[1-3,14] with 5 and 10-year biochemical disease free survival rates comparable to radical prostatectomy and external beam radiotherapy.[3] Iodine-125 and Palladium-103 are currently the most commonly used radionuclides in prostate brachytherapy. Prostate brachytherapy is a minimally invasive treatment with a quick return to full activity, and is associated with a low risk of long term morbidity.[14,15] Prostate brachytherapy, however, can be accompanied a marked increase in lower urinary tract symptoms after the procedure, and these symptoms can persist for 1 to 2 years.[16-19]

TABLE 3. **Mean pre- and 3-month post-treatment PSA levels in patients with low and intermediate risk prostate cancer**

	Low risk			Intermediate risk		
	^{125}I	^{131}Cs	p value	^{125}I	^{131}Cs	p value
Mean (SD) pre-treatment PSA (ng/mL)	5.8 (1.9)	5.1 (1.9)	0.06	7.3 (3.8)	7.3 (2.5)	0.98
Mean (SD) 3-mo PSA(ng/mL)	1.2 (0.9)	1.0 (0.7)	0.37	1.5 (1.1)	1.2 (0.8)	0.52
Mean (SD) PSA change (ng/mL)	4.6 (2.0)	4.0 (2.0)	0.12	5.8 (3.7)	6.2 (2.9)	0.75

Cs-131 = cesium-131; I-125 = iodine-125

TABLE 4. **Dose, half-life, and average energy of common radioisotopes used for prostate brachytherapy**

Isotope	Dose (Gy)	Half-life (days)	Average energy (keV)
Cs-131	115	9.7	29
I-125	145	60	28
Pd-103	125	17	21

Cs-131 = cesium-131; I-125 = iodine-125; Pd-103 = palladium-103

Cesium-131 is now also used in prostate brachytherapy. An important proposed benefit of Cs-131 is a shorter duration of the bothersome lower urinary tract symptoms that can accompany prostate brachytherapy. Cesium-131 has a similar energy level as I-125 but a much shorter half-life (9.7 days versus 60 days), Table 4. The shorter half-life of Cs-131 may contribute to the decreased duration of the urinary morbidity. The similar energy levels of Cs-131 and I-125 result in similar seed distribution for these isotopes.[4]

Given the recent introduction of Cs-131 for use in prostate brachytherapy, long term clinical studies are limited. A phase II multi-institutional trial demonstrated the safety and efficacy of Cs-131 monotherapy in 100 patients with early stage prostate cancer. Approximately two-thirds of the patients experienced frequency, urgency, or dysuria at 2 to 4 weeks following treatment, with resolution by 4 to 6 months post-implant.[20] Rectal morbidity was noted in 34% of patients, decreasing to 3% by the end of the first year.[20] Average PSA levels measured at 0, 1, 2, 4, and 6 months were 6.8, 3.2, 2.1, 1.4, and 1.1 ng/mL, respectively.[21] Few other studies to date have examined post-implant PSA levels in patients undergoing PB with Cs-131.

The definition of biochemical freedom from disease after prostate brachytherapy remains controversial, with several methods used both clinically and for research purposes including the ASTRO criteria, the Phoenix criteria, and the Kattan criteria.[22-24] Regardless of which definition is utilized, clearly the desired result after prostate brachytherapy is a low, non-rising PSA. The PSA nadir after prostate brachytherapy may take between 2 and 4 years to occur.[25] The present study does not attempt to predict long term outcome after Cs-131 prostate brachytherapy, but rather to simply compare initial PSA outcomes in men undergoing prostate brachytherapy with I-125 to Cs-131. The purpose of this study is to aid practitioners of Cs-131 prostate brachytherapy as they follow their patients after the procedure. By comparing initial PSA outcomes in Cs-131 with initial PSA outcomes in our initial I-125 PB patients, we hope to provide practitioners of prostate brachytherapy who have experience with I-125 brachytherapy information as to what to expect in terms of initial PSA outcomes in men undergoing PB with Cs-131.

Limitations of the current study include the lack of randomization, which can lead to selection bias. Additionally, there were differences in the proportions of patients meeting low and intermediate risk criteria, but these differences were not significant and did not appear to affect our overall initial PSA outcomes. Since the first 100 patients undergoing prostate brachytherapy with I-125 did not include those with high risk disease, the present study was unable to compare initial PSA outcomes in high risk patients undergoing prostate brachytherapy with Cs-131 and I-125. Direct comparison of dosimetry calculated at differing time intervals is also problematic. Without standardization, variations in the contouring of prostate volumes can influence analyzed dosimetric parameters which are influenced by the volume of the prostate contoured.[26] The effect of trauma induced post-implant edema is most significant for Cs-131, because most of the doses delivered by the Cs-131 seeds are during the period when the prostate is swollen. Therefore, dosimetry for Cs-131 seeds was performed at day 0 to minimize the deviation of the actual dose from the calculated dose. Additionally, these results represent the early experience with CS-131 at our institution. Larger patient numbers will be available as our experience with Cs-131 continues which will allow us to confirm these findings in a larger cohort of patients.

The Cesium Advisory Group (CAG) recently released consensus recommendations for Cs-131 prostate brachytherapy dosing, source strength, and source placement based on three clinical trials and more than 1,200 Cs-131 implants.[4] However, limited clinical outcomes have been published to date. Given the much shorter half-life and different dose kinetics of Cs-131, we hypothesized that the initial PSA response would be different than in patients receiving I-125. However, among our cohort, monotherapy with Cs-131 and I-125 implants for low and intermediate risk prostate adenocarcinoma produced equivalent reduction in PSA levels 3 to 6 months following treatment. Given the short follow up period, the current study was not designed to measure oncologic efficacy, however, a number of studies have demonstrated the importance of early PSA values following prostate brachytherapy. A "first" PSA value greater than 1.0 ng/mL to ≤ 4.0 ng/mL was the only independent variable identified on multivariate analysis to affect local relapse-free survival.[12] Additionally, in

patients with PSA ≤ 0.20 ng/mL at 6-12 months post-implantation, disease free survival at 48 months following implantation was 96%.[11] Among patients treated with external beam radiation therapy and a brachytherapy boost, a different population than the current cohort, post-treatment PSA (performed within 4 months of therapy) ≤ 4.0 ng/mL was a significant predictor of biochemical freedom from recurrence.[27] Finally, first post-implant PSA and PSA velocity have been shown to be strong predictors of PSA spike following brachytherapy, and patients with PSA progression display significantly different PSA kinetics than those with a spike.[10]

Given the paucity of data available in men undergoing brachytherapy with Cs-131, the present study serves as a guide for practitioners and patients. The aim of the present study is not to predict long term outcome after Cs-131 prostate brachytherapy, but rather to simply compare initial PSA outcomes in men undergoing prostate brachytherapy with I-125 and Cs-131. Despite a different half-life and dose kinetics, Cs-131 produced equivalent reduction in PSA levels 3 to 6 months following treatment compared to I-125. Long term data are needed to investigate durable clinical response. □

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