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Prostate-specific antigen density is predictive of outcome in suboptimal prostate seed brachytherapy

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ABSTRACT

PURPOSE: In prostate seed brachytherapy, a D_{90} of <130 Gy is an accepted predictive factor for biochemical failure (BF). We studied whether there is a subpopulation that does not need additional treatment after a suboptimal permanent seed brachytherapy implantation.

METHODS AND MATERIALS: A total of 486 patients who had either BF or a minimum followup of 48 months without BF were identified. BF was defined according to the Phoenix definition (nadir prostate-specific antigen + 2). Univariate and multivariate analyses were performed, adjusting for known prognostic factors such as D_{90} and prostate-specific antigen density (PSAD) of ≥0.15 ng/mL/cm^3, to evaluate their ability to predict BF.

RESULTS: Median followup for patients without BF was 72 months (interquartile range 56−96). BF-free recurrence rate at 5 years was 95% and at 8 years 88%. In univariate analysis, PSAD and cancer of the prostate risk assessment score were predictive of BF. On multivariate analysis, none of the factors remained significant. The best prognosis had patients with a low PSAD (<0.15 ng/mL/cm^3) and an optimal implant at 30 days after implantation (as defined by D_{90} ≥ 130 Gy) compared to patients with both factors unfavorable ($p = 0.006$). A favorable PSAD was associate with a good prognosis, independently of the D_{90} (<130 Gy vs. ≥130 Gy, $p = 0.7$).

CONCLUSIONS: Patients with a PSAD of <0.15 ng/mL/cm^3 have little risk of BF, even in the case of a suboptimal implant. These results need to be validated in other patients' cohorts.

Keywords: Prostate cancer; Risk biochemical failure; Brachytherapy; PSA density

Introduction

The efficacy of prostate seed brachytherapy (PB) has been proven for low- and intermediate-risk prostate cancer (1, 2). An accepted predictive factor for biochemical failure (BF) is the D_{90} (the minimal dose received by 90% of the prostate), typically measured 30 days posttreatment with a threshold of ≥130 Gy (3, 4).

Several days, if not weeks, may be required to evaluate the quality of an implant through CT scanning. Although the D_{90} may be measured on the day of the implant in some patients, the majority of patients do not undergo D_{90} assessment until 30 days postimplant. At this point, most physicians are reluctant to repeat the procedure in the case of a suboptimal implant and adopt a watch-and-wait approach instead.

In our hospital center, we do not routinely conduct reimplantation for suboptimal implants; nevertheless, we have observed a high cure rate among these patients in daily practice. Consequently, this has led to validation of our active surveillance approach to management of suboptimal implants. The purpose of this study was to evaluate factors that may predict positive outcome without further treatment.

Our hypothesis was that a suboptimal implant would have no detrimental effect on BF if prostate-specific antigen density (PSAD) was favorable (<0.15 ng/mL/cm^3).

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PSAD was chosen because of its ability to predict aggressive disease at prostatectomy (5, 6).

Methods

Eligible patients were treated in our center with low-dose-rate PB between July 2005 and September 2014. Patients with either a BF or a minimum followup of 48 months without BF were included. Patients were stratified according to the D'Amico risk classification system and had either low-risk (prostate-specific antigen [PSA] ≤10.0 ng/mL, Gleason score 2−6, and Stage T1−T2a) or lower-tier intermediate−risk (mostly only one intermediate risk factor, Gleason score ≤3 + 4, and ≤50% positive biopsies) prostate cancer. Neoadjuvant androgen deprivation therapy was very rarely used. External beam radiotherapy was added in the presence of >1 intermediate risk factors or Gleason score 4 + 3. The brachytherapy technique has been described previously (7). In brief, we used a transrectal ultrasound TRUS-guided, three-dimensional intraoperative interactive planning with virtual needle guidance, robotic seed delivery, and needle retraction system (FIRST; Elekta). The prescribed dose was 144−160 Gy. All implants were done with ^{125}I seeds.

BF was defined according to the Phoenix definition (nadir PSA + 2). Minimum followup without BF was at least 48 months.

Day 30 dosimetry was evaluated mostly on CT with 3-mm thick slices. MRI coregistration was used from January 2014 on. There were no contouring guidelines. As patients with a suboptimal implantation were not reimplanted, they were followed very closely with PSA and imaged and biopsied at very low PSA levels if suspicious of BF. These patients were then evaluated for a reimplant or salvage surgery.

This study was approved by our ethical review board.

Univariate and multivariate analyses were conducted to evaluate the predictive value of various factors of cancer aggressiveness, including suboptimal implantation (as defined by D_{90} < 130 Gy) and unfavorable PSAD (as defined by a preoperative PSA level divided by prostate volume at implantation of ≥0.15 ng/mL/cm^3).

Survival analyses were performed using the Kaplan−Meier method, and comparisons were made using the log-rank test. Multivariate analysis was done using the Cox regression model. Statistical significance was defined as p-values ≤ 0.05. Statistical analysis was done using SPSS 17.0 for Windows (IBM SPSS, Chicago, IL).

Results

Patient characteristics are shown in Table 1. A total of 486 patients had a followup of at least 48 months and were included in this study. Median followup without BF was 72 months (range for patients without BF 48−132 months, interquartile range 56−96). Twenty-five patients (5%) received a combination of external beam radiotherapy and PB, and only 1% received concomitant androgen deprivation therapy.

Table 1
Patient characteristics

N = 486	Proportion of patients (%)	Median (IQR)	CAPRA points
Stage (T category)			
T1c	74		0
T2a	23		0
T2b−c	3		0
T3	0		1
Prostate volume (cc)		36 (30−44)	
≤20	2		
21−49	86		
≥50	12		
PSA density (ng/mL/cm^3)		0.146 (0.10−0.194)	
>0.15	50.3		
D_{90} (Gy)		157 (141.3−176.0)	
PSA (ng/mL)		5.8 (4.4−7.5)	
<6	54		0
6−10	39		1
0.1−20	7		2
20.1−30	0		3
>30	0		4
Gleason score (primary/secondary grade)			
1−3/1−3	68		0
1−3/4−5	28		1
4−5/1−5	5		3
Proportion of positive biopsy cores (%)		33 (17−50)	
<34	63		0
≥34	37		1
Age at diagnosis (y)		65 (61−70)	
<50	1		0
≥50	99		1

PSA = prostate-specific antigen; IQR = interquartile range; CAPRA = Cancer of the Prostate risk Assessment Score.

Actuarial BF-free survival according to the Phoenix definition was 95% at 5 years and 88% at 8 years.

Univariate analysis revealed that several factors, including PSAD and Cancer of the Prostate risk Assessment Score (CAPRA), were predictive of BF. On multivariate analysis, none of the factors remained a significant predictive factor (Table 2).

Predictive value of various prognostic factors was assessed. Larger prostate volume was associated with better implant quality (correlation with the D_{90}: r = 0.24, p < 0.001) and lower PSAD (r = −0.42, p < 0.001). There was an inverse correlation between the D_{90} and PSAD (r = −0.26, p < 0.001).

Finally, we investigated the hypothesis that patients with a suboptimal implant (D_{90} < 130 Gy) would have less BF if the PSAD was favorable (<0.15 ng/mL/cm^3). This was not the case: Patients with a suboptimal implant and PSAD <0.15 ng/mL/cm^3 (n = 24) did not fare worse than a