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Relationship between Day 0 dosimetric parameters and biochemical relapse-free survival in patients treated with transperineal permanent prostate interstitial brachytherapy with ^{125}I seeds

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ABSTRACT

OBJECTIVES: To determine the relationship between dosimetric parameters obtained on postimplantation Day 0 and biochemical relapse-free survival (bRFS) in patients treated with ^{125}I transperineal interstitial permanent prostate brachytherapy (TIPPB).

METHODS: Two-hundred twenty men with low-risk ($n = 155$, 70.4%), low-volume intermediate-risk ($n = 63$, 28.7%), or high-risk ($n = 2$, 0.9%) prostate cancer were treated with TIPPB between December 2000 and June 2006. Seventy-four (33.6%) patients received short-term (3–6 months) androgen suppression therapy before TIPPB. The median followup for patients free of biochemical failure was of 37.9 months (range, 24.0–84.5 months).

RESULTS: The receiver operating characteristic (ROC) analysis established a best-fit cutoff value for the quantifiers D_{90} and V_{100} of 147 Gy and 92%, respectively. The Kaplan–Meier analysis of bRFS at the cutoff value of $D_{90} = 147$ Gy using the ASTRO, nadir + 2, and combined (ASTRO and nadir + 2) definitions showed a trend toward statistical significance for the ASTRO ($p = 0.076$) and nadir + 2 ($p = 0.064$) definitions and a statistically significant correlation for the combined definition ($p = 0.033$). The corresponding 7-year bRFS for the $D_{90} > 147$ Gy and $D_{90} \leqslant 147$ Gy subsets using the ASTRO, nadir + 2, and combined definitions were 96.5% vs. 89.7% (ASTRO, $p = 0.076$); 93.7% vs. 70.5% (nadir + 2, $p = 0.064$); and 94.4 vs. 75.5% (combined, $p = 0.033$). The V_{100} (%) cutoff value of 92% predicted by the ROC analysis was not significant. Among other cutoff values, only $D_{90} = 140$ Gy ($p = 0.050$) and $D_{90} = 160$ Gy ($p = 0.098$) showed a trend toward statistical significance when the nadir + 2 and the ASTRO definitions were used. The rest of dosimetric, tumor, and patient parameters did not show statistical correlation with bRFS in the Kaplan–Meier analysis.

CONCLUSIONS: The cutoff value of $D_{90} = 147$ Gy obtained on postimplantation Day 0 showed a trend toward significant correlation with bRFS when the standard ASTRO and nadir + 2 definitions were used and a weak but statistically significant correlation with bRFS as per the nonstandard combined definition in a series of patients with predominantly low-risk disease (70.4%) treated at high radiation doses (median $D_{90} = 152.9$ Gy, median $V_{100} = 92.5\%$).

Keywords: Brachytherapy; Prostate cancer; ^{125}I; Monotherapy; Implant quality; Quantifiers; D_{90}; V_{100} (%)

Introduction

The relationship between implant quality and biochemical relapse-free survival (bRFS) has been documented in several institutional and multi-institutional studies (1–7). Stock *et al.* (1) first reported a significant correlation between implant quality (defined as $D_{90} \geqslant 140$ Gy TG43 for ^{125}I) and the 4-year bRFS in a series of 134 patients treated with ^{125}I transperineal permanent prostate interstitial brachytherapy (TIPPB) as monotherapy. This finding

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as well as others prompted American and European scientific societies to recommend routine postimplant dosimetric evaluation of the prostate and organs at risk (OAR) in those men undergoing TIPPB (8, 9).

Since the seminal work by Stock *et al.* (1), other cutoff dose points and dosimetric quantifiers predictive of bRFS have emerged. For instance, D_{90} cutoff dose values of 80 (5), 100 (3), 130 (4, 7), 160 Gy (2), as well as V_{100} of 80% (5) and 90% (6), have also been reported as being predictive of bRFS (Table 1).

The vast majority of the quantifiers reported have been obtained on postplanning computerized tomography (CT) performed 2–4 weeks after the procedure (1–5, 7). Only Wallner *et al.* (6) have reported predictive quantifier data obtained on the same day of the implant. The date at which postplanning is performed is an important issue, as it is well known that $D_{90,}$ as well as other quantifiers, change over time because of the dynamics of the postimplantation prostatic edema; and, therefore, predictive cutoff values obtained at variable time points after brachytherapy may not be valid at other time points. For instance, D_{90} values calculated on Days 30–60, which are assumed to represent a stable dosimetry in most of the cases, are on average 10–15% greater than the D_{90} values calculated on Day 0 (10, 11). It is therefore imperative to find out not only reliable cutoff dose points, but also cutoff dose points at different time points. From the practical point of view, some centers prefer to perform the postplanning CT on Day 0; therefore, cutoff values are also needed at this time point.

The present study follows the work previously reported by Wallner *et al.* (6) in an attempt to correlate several Day 0 quantifiers with the bRFS curves obtained according to several definitions of biochemical failure in a series of patients with prostate cancer treated at a single institution with ^{125}I TIPPB as monotherapy.

Methods and materials

Patient selection

From December 2000 to June 2006, 220 men with a median age of 66 years (range, 42–78 years) and presenting with low-risk prostate cancer or low-volume intermediate-risk or high-risk prostate cancer underwent seed implantation with ^{125}I as monotherapy at the Clínica Universidad de Navarra, Spain. Risk groups were defined according to the National Comprehensive Cancer Network criteria (12). Low-volume intermediate-risk patients were defined as those men presenting with one single intermediate-risk factor: pretreatment prostate specific antigen (PSA) value of 10–20 ng/mL, Gleason score of 7, or American Joint Committee on Cancer stage T2b. Low-volume high-risk patients were defined as those men presenting extracapsular extension at MRI (T3a), pretreatment PSA value of less than 10 ng/mL, and Gleason score equal or less than 6. The clinical characteristics of the 220 patients are shown in Table 2.

Table 1
^{125}I quantifiers predictive of biochemical relapse-free survival

Quantifier	Cutoff value	Definition	Author	Postplanning
D_{90}	80 Gy	ASTRO (14)	Robert *et al.* (5)	Day 30
D_{90}	100 Gy	ASTRO (14)	Papagikos *et al.* (3)	Day 30
D_{90}	130 Gy	ASTRO (14)	Zelefsky *et al.* (7)	Days 0–30
D_{90}	[a]130 Gy	Kattan (18)	Potters *et al.* (4)	Days 14–21
D_{90}	140 Gy	See footnote[b]	Stock *et al.* (1)	Day 30
D_{90}	160 Gy	Nadir + 2 (15)	Linstadt *et al.* (2)	Day 30
V_{100}	80%	ASTRO (14)	Papagikos *et al.* (3)	Day 30
V_{100}	90%	See footnote[c]	Wallner *et al.* (6)	Day 0

[a] Ninety percent prescription dose.
[b] Failure defined as two consecutive rises in prostate specific antigen or a nadir level above 1.0 ng/mL.
[c] Failure defined as nadir level above 0.5 ng/mL.

All the patients were initially evaluated with a complete medical history, physical examination, and pretreatment serum PSA. Although not formally required, most patients underwent metastatic work-up with abdominopelvic CT scan, bone scan, and, in some cases, pelvic MRI.

Implant technique and postplanning

CT-based preplanning was done in all cases to determine the total isotope activity required, as well as the seed

Table 2
Tumor characteristics

Characteristics	*n* (%)
American Joint Committee on Cancer stage	
T1–T2a	212 (96.4)
⩾T2b	8 (3.6)
Pretreatment prostate specific antigen (ng/mL)	
0–9.9	170 (77.3)
⩾10	50 (22.7)
Gleason's score	
⩽6	213 (96.8)
7	7 (3.2)
Biopsy cores	
Bilateral	36 (16.4)
Unilateral	184 (83.6)
⩾50% positive[a]	1 (36.8)
<50% positive	139 (63.2)
Perineural involvement	
Yes	5 (2.3)
No	215 (97.7)
National Comprehensive Cancer Network category	
Low risk	155 (70.4)
Intermediate risk	63 (28.7)
High risk	2 (0.9)
Preimplant androgen suppression therapy	
No	146 (66.4)
Yes	74 (33.6)

[a] In at least one lobe.