

The impact of body mass index on dosimetric quality in low-dose-rate prostate brachytherapy

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Abstract

Purpose: Low-dose-rate (LDR) brachytherapy has been established as an effective and safe treatment option for men with low and intermediate risk prostate cancer. In this retrospective analysis, we sought to study the effect of body mass index (BMI) on post-implant dosimetric quality.

Material and methods: After institutional approval, records of patients with non-metastatic prostate cancer treated in Puerto Rico with LDR brachytherapy during 2008-2013 were reviewed. All patients were implanted with ¹²⁵I seeds to a prescription dose of 145 Gy. Computed tomography (CT) based dosimetry was performed 1 month after implant. Patients with at least 1 year of prostate-specific antigen (PSA) follow-up were included. Factors predictive of adequate D₉₀ coverage (≥ 140 Gy) were compared via the Pearson χ^2 or Wilcoxon rank-sum test as appropriate.

Results: One-hundred and four patients were included in this study, with 53 (51%) patients having a D₉₀ ≥ 140 Gy. The only factor associated with a dosimetric coverage detriment (D₉₀ < 140 Gy) was BMI ≥ 25 kg/m² ($p = 0.03$). Prostate volume ($p = 0.26$), initial PSA ($p = 0.236$), age ($p = 0.49$), hormone use ($p = 0.93$), percent of cores positive ($p = 0.95$), risk group ($p = 0.24$), tumor stage ($p = 0.66$), and Gleason score ($p = 0.61$) did not predict D₉₀.

Conclusions: In this study we show that BMI is a significant pre-implant predictor of D₉₀ (< 140 Gy vs. ≥ 140 Gy). Although other studies have reported that prostate volume also affects D₉₀, our study did not find this correlation to be statistically significant, likely because all of our patients had a prostate volume < 50 cc. Our study suggests that in patients with higher BMI values, more rigorous peri-implant dosimetric parameters may need to be applied in order to achieve a target D₉₀ > 140 Gy.

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Purpose

Prostate cancer is known to be the leading cause of malignancy and the second leading cause of cancer-related death among men. In 2015 alone, approximately 220,800 men were diagnosed with prostate cancer in the United States, making up about one-quarter of new cancer diagnoses [1]. Various epidemiologic studies have found a correlation between obesity and an increased risk of certain cancers [2,3]. In addition, it has been reported that obese men have a greater risk of prostate cancer-related death [3]. Based on body mass index (BMI), an indicator of obesity, more than 1 in 3 adults in the United States are considered obese. Obesity has been associated with an increased risk of biochemical failure after treatment for prostate cancer [4]. In addition to its association with biochemical failure after treatment, studies have also found an association between increased BMI and an advanced prostate tumor stage [5]. Furthermore, in a recently pub-

lished study, patients with an elevated BMI were found to have a higher rate of adverse pathologic features such as extraprostatic extension and positive surgical margins [6]. With the high prevalence of both prostate cancer and obesity, the importance of adjusting current treatment modalities for obese patients with prostate cancer has become crucial for achieving long-term biochemical control in this cohort of patients.

Current treatment techniques for prostate cancer include radical prostatectomy, external beam radiation therapy, and brachytherapy. Among these treatment modalities, low-dose-rate (LDR) brachytherapy has been established as an effective and safe treatment option for men with low and intermediate risk prostate cancer. The dose delivered to 90% of the prostate volume, or D₉₀, which is obtained through a computed tomography (CT) based post-implant dosimetric analysis, has been used as a measure of implant quality and has been found to be

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a strong predictor of outcome among men treated with LDR brachytherapy [7]. Although a $D_{90} > 130$ Gy is considered adequate by the American Brachytherapy Society [8], various studies have shown that a $D_{90} \geq 140$ Gy is associated with improved biochemical control [9,10]. Previous studies have found that specific factors such as prostate volume, post-implant prostatic edema, and the number of seeds implanted can influence D_{90} [11,12,13].

Identifying factors that lead to suboptimal dosimetric outcomes are important in order to improve implant quality as well as clinical outcomes. In this retrospective analysis, we sought to study the effect of BMI on post-implant dosimetric quality, specifically D_{90} .

Material and methods

Patients

After institutional approval, records of patients with non-metastatic prostate cancer treated in Puerto Rico with LDR brachytherapy during 2008-2013 were reviewed. Data from 104 Hispanic prostate cancer patients treated with LDR brachytherapy as monotherapy were analyzed retrospectively. All patients were implanted with ^{125}I seeds to a prescription dose of 145 Gy to the prostate with a 3-5 mm margin. The BMI for all patients was calculated based on their weight prior to seed implantation at the time of pre-planning transrectal ultrasonography (TRUS). Hormonal therapy was used 3 months prior to pre-planning TRUS for cytoreduction purposes only for those patients with an initial prostate volume > 50 cc.

Treatment planning

A pre-planning technique was used with prostate mapping performed 2-4 weeks prior to seed implantation by TRUS [14]. Ultrasound images were acquired with patients in the extended lithotomy position. All treatment planning was conducted on the Panther Brachy Treatment Planning System (Prowess Inc., Concord, CA, USA). ^{125}I loose seeds with a dose rate constant of 0.981 cGy/h/U (IsoAid Advantage, Port Richie, FL, USA) were placed transperineally under TRUS 5 mm apart from each other [15]. The seed implantation procedure was performed under epidural anesthesia with the patient in the extended lithotomy position lying in the same gurney as in the pre-planning TRUS. Dosimetric goals were as follows: $V_{100} > 95\%$, $V_{150} \leq 50\%$, and $D_{90} > 100\%$ of the prescription dose. Computed tomography based dosimetry was performed 1 month after implant and was used to determine D_{90} , defined as the dose received by 90% of the prostate. All CT-based contours were performed, reviewed, and approved by the same experienced radiation oncologist. Patients with at least 1 year of PSA follow-up were included.

Statistical methods

Factors associated with adequate D_{90} coverage ($D_{90} \geq 140$ Gy vs. $D_{90} < 140$ Gy) were determined by the Pearson χ^2 or Wilcoxon rank-sum test as appropriate. The factors evaluated for adequate D_{90} coverage include pros-

tate volume (cc), BMI (kg/m^2), initial PSA (ng/ml), age (years), hormone use, percent of cores positive, NCCN risk group (low vs. intermediate vs. high vs. unknown), tumor stage, and Gleason score (GS). A receiver operating characteristic (ROC) analysis was used to determine optimal predictive cut-off points for linear variables associated with D_{90} on univariate analysis (UVA).

Biochemical failure was defined based on the Phoenix definition (ASTRO consensus statement) [16], which is a rise in PSA ≥ 2 ng/ml above the nadir following treatment. Number of biochemical failures was compared via Pearson χ^2 . Freedom from biochemical failure (FFBF) is defined as time from implant to date of biochemical failure or last follow-up. Freedom from biochemical failure distribution was estimated using the Kaplan-Meier method and was compared via a log-rank test. Two-sided p -values and the level of significance of 0.05 were used for statistical analyses. All analyses were performed using SPSS version 22 (IBM, Armonk, NY, USA).

Results

Patient characteristics

The median follow-up of this study is 33 months (14 to 64 months). There were a total of 104 patients overall, of which 53 (51%) patients have a $D_{90} \geq 140$ Gy. The majority of the patients were GS 6 ($n = 90$, 87%) with a median initial PSA of 4.7 ng/ml. The median age was 66 years, with a median prostate volume of 29 cc (Table 1).

Predictors of adequate dose coverage

The factors associated with D_{90} (< 140 Gy vs. ≥ 140 Gy) are illustrated in Table 2. The only factor associated with inadequate D_{90} coverage (< 140 Gy) was higher BMI (median: 28.3 vs. 26.7 kg/m^2 , $p = 0.023$). Prostate volume ($p = 0.26$), initial PSA ($p = 0.236$), age ($p = 0.49$), hormone use ($p = 0.93$), percent of cores positive ($p = 0.95$), NCCN risk group ($p = 0.24$), tumor stage ($p = 0.66$), and Gleason score ($p = 0.61$) were not associated with D_{90} .

Biochemical failure

There were a total of 6 (5.8%) biochemical failures in this study, with a 5-year freedom from biochemical failure of 90.8% (Figure 1). $D_{90} \geq 140$ Gy was not associated with a significant difference in biochemical failure (7.5% vs. 3.9%, $\chi^2 p = 0.43$) or 5-year freedom from biochemical failure (90% vs. 91.3%, log-rank $p = 0.53$), when compared to $D_{90} < 140$ Gy. Categorical BMI showed that overweight (BMI ≥ 25 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) were not associated with 5-year freedom from biochemical failure ($p = 0.19$ and $p = 0.95$).

Discussion

The management of prostate cancer comprises a broad spectrum of treatment modalities. Prostate brachytherapy, specifically LDR brachytherapy, has been used for many years as an effective and safe treatment option for low and intermediate risk prostate cancer patients. In our

Table 1. Patient characteristics (N = 104)

Factor	Median (range)
Age (years)	66 (52-84)
BMI (kg/m ²)	27.2 (18.1-48.4)
Initial PSA (ng/ml)	4.7 (0.6-19.7)
Prostate volume (cc)	29 (11-48)
Follow-up (months)	33 (14-64)
	n (%)
BMI	
< 25 kg/m ²	71 (68)
≥ 25 kg/m ²	18 (17)
Unknown	15 (14)
NCCN risk group	
Low	80 (77)
Intermediate	21 (20)
High	1 (1)
Unknown	2 (2)
Tumor stage	
T1c	85 (82)
T2a	8 (8)
T2b	7 (7)
T2c	4 (4)
Gleason score	
5	6 (6)
6	90 (87)
7	7 (7)
≥ 8	1 (1)
Percent of cores positive	
< 50%	94 (90)
≥ 50%	10 (10)
Unknown	0 (0)
D₉₀ (> 140 Gy)	
< 140 Gy	51 (49)
≥ 140 Gy	53 (51)
Hormone therapy	
No	86 (83)
Yes	18 (17)
Biochemical failure	
No	98 (94)
Yes	6 (6)

BMI – body mass index, PSA – prostate-specific antigen, NCCN – National Comprehensive Cancer Network, D₉₀ – the minimum dose received by 90% of the prostate volume

Table 2. Factors associated with adequate dosimetric coverage

Characteristics	< 140 Gy (n = 51)	≥ 140 Gy (n = 53)	UVA (p)
	Median (range)	Median (range)	
BMI (kg/m ²)	28.3 (20.5-37.3)	26.7 (18.1-48.4)	0.023
Age (years)	66 (52-84)	66 (53-80)	0.487
Prostate volume (cc)	30 (14-45)	26 (11-48)	0.261
Initial PSA (ng/ml)	5.05 (1.31-19.7)	4.69 (0.64-11.38)	0.236
	n (%)	n (%)	
NCCN risk group			
Low	36 (71)	44 (83)	0.241
Intermediate	12 (24)	9 (17)	
High	1 (2)	0%	
Unknown	2 (4)	0%	
Tumor stage			
T1c	43 (84)	42 (79)	0.656
T2a	3 (6)	5 (9)	
T2b	4 (8)	3 (6)	
T2c	1 (2)	3 (6)	
Gleason score			
5	2 (4)	4 (8)	0.611
6	44 (86)	46 (87)	
7	4 (8)	3 (6)	
≥ 8	1 (2)	0 (0)	
Percent of cores positive			
< 50%	46 (90)	48 (91)	0.949
≥ 50%	5 (10)	5 (9)	
Hormone therapy			
No	42 (82)	44 (83)	0.928
Yes	9 (18)	9 (17)	

BMI – body mass index, PSA – prostate-specific antigen, NCCN – National Comprehensive Cancer Network, D₉₀ – the minimum dose received by 90% of the prostate volume

study we evaluated the effect of pre-implant factors on D₉₀ and chose a D₉₀ ≥ 140 Gy as our cutoff point because various studies have shown better outcomes in patients treated with a D₉₀ ≥ 140 Gy. In a large single institution series of 1,298 patients, Henry and colleagues reported excellent biochemical control outcomes in low and intermediate risk patients treated with LDR brachytherapy, particularly those treated with a D₉₀ ≥ 140 Gy [9]. This study reported biochemical control of 88% in patients with a D₉₀ ≥ 140 Gy vs. 78% in patients with a D₉₀ < 140 Gy.

Kollmeier *et al.* also described excellent biochemical control outcomes in patients with optimal dosimetry and reported a 94% 8-year freedom from biochemical failure in patients with low-risk prostate cancer treated with a $D_{90} \geq 140$ Gy [10]. Studies like these not only established the effectiveness of LDR brachytherapy but also elucidated the importance of post-implant dosimetry and understanding the factors that can affect this. In addition to its effectiveness LDR brachytherapy is also associated with low morbidity. Given the commonly indolent nature of prostate cancer and the excellent outcomes among patients, the importance of using treatment modalities associated with low morbidity becomes crucial. Stock and colleagues found a low incidence of lower urinary tract symptoms in patients treated with LDR brachytherapy and reported that only 4% of these patients required a Foley catheter for 24-48 hours post-implant and only 2% required a transurethral resection of the prostate [17]. Furthermore, they also reported that erectile function was not affected in the majority of patients.

Because dosimetric quality is strongly correlated with biochemical failure, various studies have looked at pre-implant factors that affect D_{90} . Although pre-implant planning is done using TRUS, after implantation CT-based images are used for dosimetric analysis. In a retrospective review of 210 patients, Sugawara *et al.* found the use of neoadjuvant hormonal therapy to be negatively associated with D_{90} , whereas prostate volume and total radioactivity positively influenced post-implant D_{90} [18]. In addition to prostate volume, prostatic edema, and the number of seeds implanted, Stock *et al.* found that CT/US volume ratio had the greatest association with D_{90} and reported that patients with a greater CT/US ratio had a lower D_{90} [11].

In this study we analyzed the effect of BMI on post-implant dosimetric quality, specifically D_{90} . Statistical analysis revealed that an increased BMI is a significant pre-implant factor which negatively affects D_{90} (< 140 Gy vs. ≥ 140 Gy). Although other studies have reported that prostate volume also affects D_{90} , our study did not find this correlation to be statistically significant, likely because all of our patients had a prostate volume < 50 cc. Previous studies analyzing implant quality have reported a tendency for lower doses to be delivered anteriorly as compared to the posterior prostate in patients treated with LDR brachytherapy [19,20]. In a multi-institutional analysis of 4547 patients, Merrick *et al.* found that the V_{100} was less at the base (51.5%) and anterior (45.7%) of the gland when compared to the lateral (68.8%), posterior (75%), and mid gland (65.9%) [21]. We postulate that increased perirectal and periprostatic fat in patients with higher BMI values may lead to difficulties accessing the anterior prostate, thereby resulting in an inferior D_{90} .

Other studies have found an association between BMI and rectal dosimetry, further illustrating the potential effect of adipose tissue in the prostate-rectum interface on dosimetric outcomes. A previous analysis of rectal dosimetry in 407 patients found that men with a higher BMI received a lower rectal wall dose as compared to those with a lower BMI [22]. Given that BMI is an indicator of adipose tissue, the authors came to the conclusion that

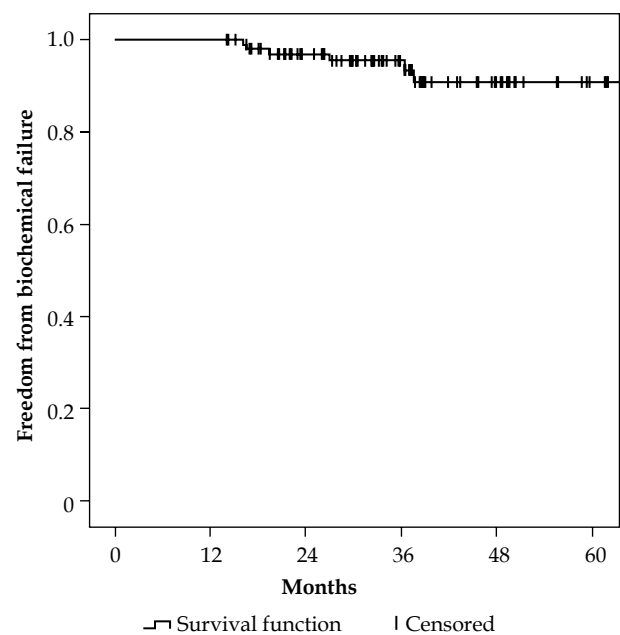


Fig. 1. Freedom from biochemical failure of the entire cohort

periprostatic fat could potentially decrease the dose received by the rectum. Tiberi *et al.* also found a negative correlation between BMI and dose to the rectum [23]. In addition to affecting rectal dose, we suggest that prostate-rectum interface adipose tissue can also have a negative effect on the anterior dose received by the prostate. In another study by Otón *et al.*, rectal distention was found to negatively affect implant dosimetry, further illustrating the impact of peri-prostatic structures on implant quality [24].

Although in our cohort of patients there was no statistically significant difference in biochemical failure between patients treated with a $D_{90} \geq 140$ Gy and those treated to a $D_{90} < 140$ Gy, we did not have an adequate patient volume to analyze this endpoint. Furthermore, the cohort of patients evaluated in this study had a limited follow-up time, which is very often seen in Puerto Rico, where the lack of physicians prevents adequate follow-up; and although a mean follow-up time of one year does not impact dosimetric quality, it may influence biochemical failure outcomes. Another limiting factor of this study is its retrospective nature and lack of dosimetric prostate sector analysis. While our results showed that BMI negatively affected dosimetric outcomes, a limitation of our study was the low number of patients included, specifically those with a BMI ≥ 25 kg/m². In this study, patient BMI was only obtained at the time of pre-planning TRUS, and because changes in BMI could potentially occur from the time of pre-planning to seed implantation, we were unable to evaluate whether these changes affected D_{90} . In the future, changes between pre-implant and post-implant BMI and the effect of these changes on dosimetric quality should be analyzed.

Now that we have shown an association between BMI and D_{90} , a future direction of this study would be to analyze the anterior prostatic dose in patients with a higher BMI and determine whether this is the cause of inferior

dosimetric outcomes in this cohort of patients. Furthermore, other institutions have shown that the use of institution-specific nomograms can facilitate the implant planning process [25]. In addition to dosimetric parameters, patient characteristics such as BMI could also be used in such nomograms, which may result in higher quality of implantation.

Conclusions

Our results show that increased BMI is associated with inferior dosimetric outcomes, specifically D_{90} . This data suggests that in order to achieve a $D_{90} \geq 140$ Gy in patients with higher BMI values, a D_{90} that is greater than the target post-implant D_{90} may need to be planned.

Disclosure

Authors report no conflict of interest.

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