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Erectile Dysfunction and Penile Bulb Dose Follo ing Definitive Prostate Radiation Therapy

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Abstract

Background: Erectile dysfunction (ED) is a common side effect of prostate cancer treatment, affecting up to 50% of patients after radiation therapy.

Objectives: This study aims to analyze the correlation bet een the dose received by the penile bulb (PB) and ED in men ho under ent definitive radiation therapy for early-stage prostate cancer ithout androgen deprivation therapy.

Methods: The study included 40 patients ho received 3D conformal radiation therapy (3D-CRT) for localized prostate cancer and ere reported to be potent before treatment, as determined by the International Index of Erectile Function (IIEF-15) questionnaire. The dose to the PB as measured using dose volume histograms (DVHs), and the IIEF-15 questionnaire as completed again 3 months after 3D-CRT. The Pearson correlation coefficient and linear regression test ere used to examine the correlation bet een the ED score and PB doses. Statistical significance as considered if the P value as less than 0.05.

Results: The mean age of the patients as 75.5 ± 5.70 years. The average ED score based on the questionnaire as 15 ± 10.55. T enty percent of the patients had moderate ED, hile 80% had mild ED (all patients reported a decrease in potency after 3D-CRT). Ho ever, the correlation bet een the ED score and the PB mean dose as not statistically significant.

Conclusions: This study revealed ED in all prostate cancer patients after 3D-CRT, but no significant correlation as found bet een the dose received by the PB and radiotherapy-induced impotence.

Keywords: Radiation Therapy, Prostate Cancer, Prostate Cancer; Penile Bulb

1. Background

Prostate cancer is the most frequently diagnosed cancer and the second most prevalent cause of cancer death in men (1). With the increased implementation of screening programs, more patients are being diagnosed at earlier stages, significantly improving their survival (2). Therefore, efforts should be made to reduce the side effects of treatment (3). Currently, treatment options for patients ith early-stage prostate cancer include active surveillance, radical prostatectomy, and definitive radiotherapy (RT) (4, 5). In many cases of early-stage prostate cancer, definitive RT is chosen due to the patient's inability to tolerate surgery or their preference for a non-surgical procedure ithout compromising the outcome (6). Ho ever, acute and late toxicities related to unintentional doses to organs at risk are expected follo ing RT administration (7).

Erectile dysfunction (ED), defined as the inability to obtain or maintain a penile erection during sexual activities, is a common problem associated ith prostate RT, ith an estimated rate of up to 50% in some reports (8). The underlying mechanisms may include direct radiation-induced damage to the penile bulb (PB)

or the neurovascular bundles, although the exact mechanisms remain unclear (9-11). The rates of ED follo ing definitive RT have decreased in recent years ith the advancement of treatment techniques (12). Conformal treatment technologies, such as intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), and stereotactic body radiotherapy (SBRT), have improved the technical delivery and dose administered by radiation therapy, thereby reducing acute and late side effects (13-15).

These advanced techniques have made it possible to increase the doses to targeted areas hile reducing the dose to at-risk organs (14, 16, 17). The PB is located near the prostate and the radiation field. The dose received by the PB is a crucial factor in the development of ED, ith a dose of approximately 50 Gray (Gy) to the entire PB identified as a threshold for an increased risk of ED (13, 18). In many oncological centers in Iran and similar developing countries, 3-dimensional conformal radiotherapy (3D-CRT) is the most commonly available method. Ho ever, there is limited data on the dose to the PB and its association ith sexual disorders related to prostate radiation therapy in Iran.

2. Objectives

This study aims to investigate the relationship bet een the PB dose in 3D-CRT and the incidence of ED related to RT at the Mahdieh and Besat Radiation Therapy Center in Hamadan, Iran.

3. Methods

The study involved patients ith lo -risk prostate cancer (PSA < 10, Gleason Score < 7, T stage < T2) ho had an expected life expectancy of more than 10 years and ere referred for definitive external beam radiation therapy (EBRT) at the Mahdieh and Besat Radiation Therapy Center in Hamadan, Iran, bet een June 2021 and August 2023. Patients ho ere candidates for concurrent or adjuvant androgen deprivation therapy (ADT) ere excluded from the study.

Individuals ith underlying health conditions kno n to increase the risk of ED, such as atherosclerosis, hypertension, diabetes, and cardiovascular disease, ere also excluded. Additionally, smokers or those ho had smoked in the past 6 months ere not included. Pelvic multiparametric MRIs ere performed on all patients to ensure appropriate staging before entering the study. All patients ere initially examined for proper erection by a trained urologist, and they completed the International Index of Erectile Function (IIEF-15) Questionnaire. The IIEF-15 consists of 15 questions that assess male sexual function across five main domains: Erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. Each question is scored from 0 to 5. Patients ere categorized based on their total score as follo s: 1 - 10: severe ED; 11 - 16: Moderate dysfunction; 17 - 21: Mild to moderate dysfunction; 22 - 25: Mild dysfunction; 26 - 30: No dysfunction. Those scoring 25 or belo ere classified as having ED before radiation therapy and ere excluded from the study.

According to Rezaee et al., the Persian version of the IIEF-15 is a valid and reliable tool for assessing male sexual function. They reported Cronbach's alpha and intra-cluster correlation coefficients for the questionnaire at 0.893 each (ith a confidence interval bet een 0.811 and 0.950), indicating strong internal consistency of the questionnaire items and domains (19). The Cronbach's alpha for our sample as 0.97. CT scans ere performed ith an empty rectum and a comfortably full bladder in the supine position. Axial CT scans ith 5 mm slice thickness ere used for contouring and ere fused ith multiplanar MRI. Clinical tumor volume (CTV), planned tumor volume (PTV), PB, rectal, and prostate anatomy ere delineated on each slice. Radiotherapy as administered exclusively to the prostate, as pelvic lymph node irradiation as deemed unnecessary due to the patients' lo risk. The prostate gland and seminal vesicles ere included as CTV. A 5 mm margin as applied in all directions for PTV, except for a 3 mm margin posteriorly to spare the rectum. The PB as defined as the proximal part of the penis, located just caudal to the prostate gland (the proximal expansion of the corpus spongiosum attached to the urogenital diaphragm and covered by the bulbospongiosus muscle).

External beam radiation therapy as planned and delivered ith the patient in the supine position. All patients under ent 3D-CRT ith a total dose of 76 Gy, administered as 2 Gy per fraction. The energy used for all patients as 18 MeV, delivered by an Elekta Synergy linear accelerator. The dose received by the PB as measured using dose-volume histograms (DVH). For each DVH, the average dose received by the PB as calculated. Three months after completing radiation therapy, patients ere asked about their sexual function during follo -up visits, and they completed the IIEF questionnaire again. Data collected included age, disease stage, mean dose to the PB, ED score, and Body Mass Index (BMI). The data ere analyzed using SPSS version 26 soft are (SPSS Inc., Chicago, IL, USA). The Pearson correlation coefficient as used to investigate

the relationship bet een ED score and dose received. A linear regression test as used to examine the adjusted association bet een the mean dose and ED. The normality of the ED response variable (measured as a continuous variable) as assessed using the Kolmogorov-Smirnov test. The linearity assumption for the regression model as checked using residual plots. Residuals (the differences bet een observed and predicted values) ere plotted against the independent variables. The residuals ere randomly scattered around zero ith no clear pattern, suggesting that the linearity assumption holds for the three variables in the model. To determine if the t o ED groups (mild versus moderate) ere homogeneous ith respect to age, BMI, and received dose, e used t o independent sample *t*-tests. All tests ere considered statistically significant hen the P value as <0.05.

4. Results

Forty patients ho under ent definitive external beam radiotherapy (EBRT) for lo -risk prostate cancer ere enrolled in this study. The mean ± SD age of the patients as 75.5 ±5.70 years, ith an age range of 68 to 85. Disease stage as I in 60% of the patients, hile the remaining 40% ere at stage IIA. The mean ± SD dose to the PB as 56.98 ± 9.05 Gy (95% CI = 50.50 - 63.46). The average ED score based on the questionnaire as 15 ± 10.55. The correlation bet een the ED score and the dose as not significant (r = -0.199; P = 0.589).

A multivariate regression analysis as conducted to investigate the association bet een ED and the received dose, adjusted for the effects of BMI and age. Table 1 presents the coefficients of the multivariate linear regression for the associations bet een the average received dose and ED. According to the results, there as no significant association bet een the average received PB dose and the ED score. Additionally, based on the categorization of ED, 20% of the patients had moderate ED, and 80% had mild ED. Table 2 sho s the doses received by the t o groups. As sho n, there ere no significant differences in the doses received bet een the t o groups.

5. Discussion

Prostate cancer is a common cancer type among men, accounting for 14.1% of all ne cancer cases and 6.8% of all male cancer deaths orld ide in 2020 (20). Radiotherapy is a critical component of curative treatment for early-stage prostate cancer, ith outcomes comparable to radical prostatectomy (21). Compared to surgery, RT offers several advantages, including avoiding complications associated ith general anesthesia and surgery, such as bleeding, and a lo er risk of urinary incontinence and stricture (22). Recent clinical trials have sho n that increasing radiation doses to the prostate can improve cancer-related outcomes, though it may also increase side effects, such as sexual disorders (23).

The incidence of ED follo ing RT varies idely, affecting 20% to 90% of patients (24). While early-stage prostate cancer patients generally have high survival rates, approximately half may develop ED ithin 3 to 5 years after completing treatment (25). Since sexual function is a crucial aspect of human health and cancer survivorship, understanding the potential effects of different treatment modalities on sexual health is essential (26). Key predictors of ED follo ing treatment include the patient's age at the time of radiation, their erectile function before treatment, the type of RT used, and the health of their erectile tissues (27). Younger men and those ith better erectile function before treatment tend to have better erectile outcomes (24). Many studies have identified patient-related factors such as diabetes, smoking, a history of hypertension, and cardiovascular disease as risk factors for ED (28). A study by Cahlon et al. involving 487 patients ho under ent prostate RT found that age over 70 years and diabetes ere significant contributors to the development of ED (29). In this study, patients ith diabetes, smokers, and those ith a history of hypertension or cardiovascular disease ere excluded. We also excluded patients receiving ADT, as ADT has been sho n to predict ED follo ing EBRT. Additionally, patients ho had undergone brachytherapy ere excluded, as the additional dosage from brachytherapy complicates the determination of the contributions of each therapy (30).

Studies on erectile function follo ing RT have mainly focused on the dose to critical erectile structures, particularly the PB (31). Many studies suggest that the maximum dose to the PB area to prevent ED should be less than 50 Gy (18). In a study by Fisch et al., hich also used 3D-CRT, 33% of patients reported ED, ith a dose of D70 ≥70 Gy significantly associated ith ED (32). Mangar et al. investigated the rate of ED based on patient-reported questionnaires and found that a D90 ≥50 Gy is associated ith a significant risk of ED (33). In the current study, the average dose to the PB as 56.98 Gy, exceeding the recommended maximum dose.

There is inconsistency regarding the relationship bet een PB dose and ED occurrence in prostate cancer (34, 35). Although the PB is a primary focus in many research studies, several investigations have sho n that the dose delivered to the PB is not the most significant

Table 1. Coefficients of Multivariate Linear Regression for the Associations Bet een Average Received Dose and Erectile Dysfunction [a]

Model		Unstandardized Coefficients		Standardized Coefficients	*t*	Sig.
		B	Std. Error	Beta		
1	(Constant)	-129.694	71.474	-	-1.815	0.120
	Dose	-0.002	0.004	-0.201	-0.603	0.569
	BMI	3.400	1.785	0.658	1.904	0.106
	Age	1.013	0.602	0.547	1.682	0.143

Abbreviation: BMI, Body Mass Index.

[a] Dependent Variable: Erectile dysfunction.

Table 2. Comparison Bet een T o Erectile Dysfunction Groups (Mild Versus Moderate) in Terms of Age, Body Mass Index, and Mean Dose

Variables	Mean ± SD	P-Value
Age		0.293
Mild	74.5 ± 5.86	
Moderate	79.5 ± 3.53	
Average received dose		0.711
Mild	57.27 ±10.23	
Moderate	55.84 ± 13.33	
BMI		0.303
Mild	23.64 ± 2.05	
Moderate	25.39 ± 1.76	

Abbreviation: BMI, Body Mass Index.

factor for ED (36). A recent systematic revie revealed that out of 23 studies on radiation-induced ED, only 15 sho ed a significant correlation bet een the PB dose and the incidence of ED (36). For instance, Roach et al. found that patients ith a median penile dose of 52.5 Gy or more had a greater risk of radiation-induced impotence compared ith those receiving a dose of less than 52.5 Gy (P = 0.039, odds ratio = 1.98, 95% CI = 1.03 - 3.78) (18). Ho ever, Van der Wielen et al. found no significant differences in mean dose, maximum dose, or volume of various structures bet een patients ith and ithout ED 2 years after EBRT (37). Similarly, Selek et al. studied 28 patients and found that 68% developed post-treatment ED, but there as no dose-volume effect bet een PB dose and ED, hich aligns ith our research findings (38).

To explain this controversy, it is important to recognize that the development of ED in prostate cancer patients is a multifaceted phenomenon influenced by various physical and psychological factors. Some studies have focused on other anatomical structures, such as the proximal centimeter of the crura, internal pudendal arteries, neurovascular bundles, and ejaculatory ducts (37). Ho ever, there as insufficient evidence to establish a relationship bet een ED and the dose to the neurovascular bundles based on eight studies. One study investigated the relationship bet een ED and the dose received by the internal pudendal arteries but found no significant correlation (36). Nevertheless, studies that spared blood vessels reported positive outcomes in maintaining erectile function ithout compromising the intended treatment volume. Thus, controversy exists regarding the importance of doses to different irradiated structures in the development of ED (36).

It has been suggested that the effects of RT on penile structures may extend beyond anatomical damage and contribute to an inflammatory process (39). Radiation therapy induces a proinflammatory cytokine cascade that creates an inflammatory microenvironment, leading to neurovascular toxicity (40). The degree of inflammation is directly proportional to the amount of irradiated prostatic tissue, fraction delivery time, patient setup errors, and rectal sparing protocols (40). Endothelial damage and accelerated atherosclerosis of various vessels in the prostate area can also occur, leading to arterial occlusive disease and abnormal blood flo , hich can affect a significant percentage of patients (40).

To achieve penile erection, psychogenic stimulation triggered by sexual thoughts and stimuli is required in addition to pathophysiological factors. For patients ith prostate cancer, ED may result from various psychological factors such as depression, anxiety, frustration, shame, and lack of confidence in sexual performance (41). Several studies have indicated that prostate cancer treatment can lead to changes in emotional state, self-esteem, and body image, hich may contribute to ED (42, 43). Therefore, to arrive at a more accurate conclusion, it is essential to assess the psychological aspects of prostate cancer treatment using appropriate questionnaires such as the Self-Esteem Scale (SES), Personal Attributes Questionnaire (PAQ), Body Image Scale (BIS), and the functional assessment of cancer therapy-prostate (FACT-P). It is orth noting that in this study, only the IIEF-15 Questionnaire as used, and this should be considered hen interpreting our conclusions.

Several limitations should be considered hen interpreting our findings. Firstly, our sample size as relatively small, hich may impact the generalizability of our results. Additionally, hile our primary focus as on exploring the relationship bet een ED and PB dose, e did not examine potential correlations ith other anatomical structures, presenting an opportunity for future research in this area. Lastly, our data collection as restricted to patient visits over a 3-month period, hich may provide only a partial understanding of long-term trends and effects. Therefore, further research ith a larger sample size and extended follo -up is needed to provide a more comprehensive understanding of the topic.

Despite advancements in radiation techniques designed to minimize nerve and vascular damage to the prostate and reduce the exposure of surrounding tissues to radiation, a recent study found that 100% of patients reported experiencing post-treatment ED. This issue may be attributed to the routine use of 3D-CRT, particularly in developing countries like Iran, hich can result in damage to normal tissue, including the PB, despite efforts to contour the organ at risk. As many medical centers in developing countries utilize 3D-CRT to treat prostate cancer, a multidisciplinary discussion may be necessary to select the most appropriate treatment modality. Considering advanced techniques such as IMRT, IGRT, volumetric modulated arc therapy (VMAT), and stereotactic body radiation therapy (SBRT) could be steps to ards improving patient outcomes.

5.1. Conclusions

According to this study, all patients experienced reduced potency ithin 3 months of receiving radiation therapy. Ho ever, further analysis did not establish a statistically significant correlation bet een the radiation dose administered to the PB and potency preservation. This aspect requires further investigation in future studies ith a larger sample size and the use of more advanced radiation techniques.

Footnotes

Authors' Contribution: Study concept and design, Zahra Keshtpour Amlashi; acquisition of data, Hamidreza Mojtahedi and Zahra Keshtpour Amlashi; analysis and interpretation of data, Leili Tapak, Maryam Kalantari Khandani, and Masoumeh Nouri; drafting of the manuscript, Maryam Kalantari Khandani and Masoumeh Nouri; critical revision of the manuscript for important intellectual content, Maryam Kalantari Khandani, Masoumeh Nouri, Zahra Keshtpour Amlashi, Seyed Alireza Javadinia; statistical analysis, Mohsen Alemi, Leili Tapak; administrative, technical, and material support, Seyed Alireza Javadinia; study supervision, Zahra Keshtpour Amlashi , Abdolazim Sedighi Pashaki.

Conflict of Interests Statement: The authors report no conflicts of interest.

Data Availability: All data generated and analyzed during this study can be accessed through direct communication ith the corresponding author and the agreement of all research team members.

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