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ARTICLE

Clinical Research

Risk of erectile dysfunction after modern radiotherapy for intact prostate cancer

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Abstract

Background Erectile dysfunction (ED) is a prevalent side effect of prostate cancer treatment. We hypothesized that the previously reported rates of ED may have improved with the advent of modern technology. The purpose of this project was to evaluate modern external beam radiotherapy and brachytherapy techniques to determine the incidence of radiotherapy (RT) induced ED.

Methods A systematic review of the literature published between January 2002 and December 2018 was performed to obtain patient reported rates of ED after definitive external beam radiotherapy, ultrafractionated stereotactic radiotherapy, and brachytherapy (BT) to the prostate in men who were potent prior to RT. Univariate and multivariate analyses of radiation dose, treatment strategy, and length of follow-up were analyzed to ascertain their relationship with RT-induced ED.

Results Of 890 articles reviewed, 24 met inclusion criteria, providing data from 2714 patients. Diminished erectile function status post RT was common and similar across all studies. The median increase in men reporting ED was 17%, 26%, 23%, and 23%, 3DCRT, IMRT, low dose rate BT, and SBRT, respectively, at 2-year median follow-up.

Conclusion ED is a common side effect of RT. Risk of post-RT ED is similar for both LDR brachytherapy and external beam RT with advanced prostate targeting and penile-bulb sparing techniques utilized in modern RT techniques.

Introduction

The diagnosis of prostate cancer is increasingly common with many options for treatment[1,2]. These treatments are quite effective, as evidenced by the more than three million prostate cancer survivors were living in the United States as of 2014[3]. Of the available management strategies, between 33% and 50% of men undergoing prostate cancer treatment choose radiation therapy (RT). Definitive RT options include low and high dose rate brachytherapy, proton therapy, and standard, moderately or severely hypofractionated photon-based EBRT.

Erectile dysfunction (ED) is a prevalent side effect of prostate cancer treatment, and is certainly not limited to the various types of RT. The development of RT-induced ED directly affects a patient's overall satisfaction with their treatment. Such effects can have far-reaching impacts on survivors' health. For example, several studies have found a significant correlation between ED and the presence of depression symptoms[4,5]. Notably, even men of advanced age report feeling very strongly about the importance of sexual function—a survey of nearly 5000 men found that 71% of men between 70 and 80 years of age reported engaging in sexual activity, with 42% having sex weekly[6]. Thus, development of RT-induced ED is a major health concern for prostate cancer survivors, and ought to be of concern to clinicians as well. Because of the high likelihood of long-term survival after prostate cancer diagnosis and treatment, modern radiotherapeutic techniques are designed to minimize damage to erectile organs and preserve an individual's quality of life (QOL). High quality prospective studies of patient such as Sanda et alreport outcomes comparing modalities and provide

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an understanding of change over time[7]. However these studies typically report aggregate questionnaire scores, rather than the likelihood of the event on a per person basis. This information is key in counseling patients about risks during treatment decision-making.

Reports describing the incidence of ED after prostate cancer treatment have predominantly reported data from older therapy techniques, before recognition of the association between ED and the RT dose delivered to the penile bulb[8]. Some studies comparing EBRT, brachytherapy (BT), and surgery have suggested a reduced rate of RT induced ED in patients undergoing BT. This difference in ED rates between RT modalities has been attributed to the physical properties of BT, which minimizes dose to organs outside of the prostate capsule[9]. Given the relative lack of literature comparing rates of RT induced ED across short, medium, and long-term follow-up periods, the aim of this study was to retrospectively evaluate and compare rates of ED after modern RT techniques (BT versus IMRT/SBRT (+3DCRT)) in order to more completely document and describe the risk/benefit profile of the various PC treatments currently available to clinicians and their patients.

Methods

A systematic review of the literature using PRISMA guidelines was performed to collect data concerning changes in patients' self-reported erectile function both before and after prostate RT. Articles published between January 2002 and December 2018 were reviewed, with PubMed being the primary database utilized in the analysis. "Erectile radiation prostate" and "sexual function radiation prostate" were used as search terms. Studies were omitted from analysis if: (1) the publication was not available in English, (2) ED was not a patient-reported outcome, (3) baseline and endpoint ED rates were not published within the study, (4) radiation dose and fractionation schedule were not provided, (5) significantly different dose schedules and/or therapies were combined when reporting outcome, and/or (5) patients received androgen deprivation therapy (ADT).

Several variables (patient sample size, mean or median age, type of radiation therapy, total RT dose, fraction size, ED outcome measurement tool used, length of follow-up, and baseline and endpoint ED rates) were extracted from the selected studies and compiled into a single dataset. If a study reported a range of RT doses (e.g. 72–74 Gy), the mean RT dose was calculated and used to represent the radiation dose used in that study.

The authors examined how the type of RT, duration of follow-up, and median total RT dose affected the change in erectile dysfunction rates over time (ΔED) using sample t-tests or univariate regressions, as appropriate. A multivariate logistic regression model (Eq. 1.1) was also fit to the data to identify how these variables jointly affected ΔED.

$$\log\frac{p_i}{1-p_i} = \mu + \alpha_B + \beta_t \text{time} + \beta_d \text{Dose} \quad (1.1)$$

Variation in ΔED_i is explained by the baseline mean μ plus the effect α_β of the type of therapy (3DCRT/IMRT versus BT versus SBRT). β_t is the effect of time post-irradiation and β_d, the effect of centered total radiation dose. The logistic regression model (1.1) was fit by the method of maximum likelihood. The baseline used IMRT data from the med ian dose and age of the entire dataset (follow-up time of 24 months and total dose of 72 Gy). For 3DCRT, SBRT and LDR BT, dose was centered at the median dose for that modality (71.1, 35.6, and 145 Gy, respectively). We also fit a second logistic regression model wherein the effect of age was added (1.1). Statistical analyses were performed using R (3.6.1), a free software environment for statistical computing and graphics.

Results

Of 890 articles initially identified, 169 were duplicates. The remaining 721 citations were reviewed first in abstract, then full-text form. Many studies were excluded because they did not state the baseline prevalence of ED or they published only instrument summary change scores for patient cohorts. Twenty-four papers met all eligibility criteria, providing data from 2714 total patients (Fig. 1)[10–33].

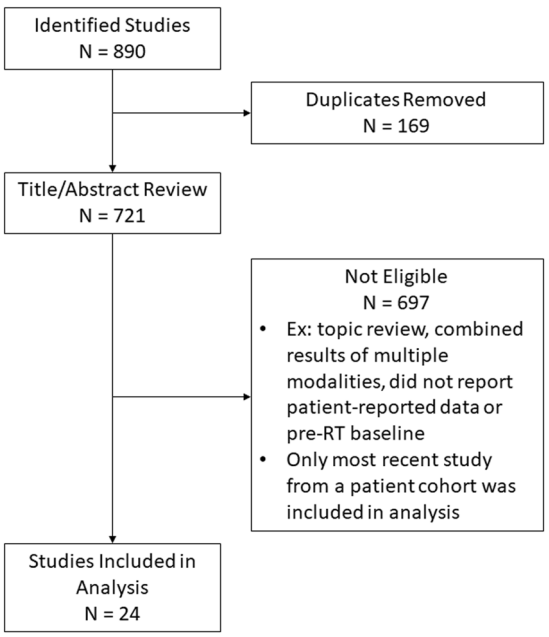

Fig. 1 PRISMA diagram of systematic identification and review of articles. Of 890 studies identified by search query, 24 articles met all eligibility criteria. The remaining were removed either because of duplicate publications or because study did not meet eligibility criteria.

Fourteen unique dose schedules were found within those 24 studies—4 studies utilizing 3DCRT, 5 with IMRT, 6 with SBRT, 11 low dose rate (LDR), 1 proton, and 1 high dose rate (HDR) BT studies were included in analyses. Of note, data from the study describing HDR BT and the study describing proton therapy were included in descriptive statistics, but not in univariate or multivariate analyses. The median follow-up time for the included studies ranged between 12 and 84 months. The compiled data are provided in Table 1 and summarized by modality in Table 2.

The EPIC (Expanded Prostate Index Composite), IIEF (International Index of Erectile Function), and the SHIM (Sexual Health Inventory for Men, a shortened version of IIEF) questionnaires were most commonly utilized to gauge the reported ΔED pre- and post-RT. ED was prevalent in this patient population prior to RT. The majority of studies did not report response rate for the questionnaires. Of the five which did, two reported rates >80%, two reported rates between 65% and 98% depending on time point, and one reported that full completion was achieved in only 20% of patients. Of the 21 studies which used validated

Table 1 Study Characteristics and ED rates.

Author	Year	Type RT	Age (mean/median)	Dose (Gy/GyE) Mean (Range)	Fractions	ED Measurement Tool	Pre-RT Potency (No ED)	Post-RT Potency (No ED)	Time of Final ED Measurement (Months)	% Change in Erectile Function (ΔED)
Valicenti[10]	2002	3DCRT	71	70.2	39	BSFI & SFI	77%	67%	12	10%
Yeoh[11]	2003	3DCRT	64	55–64	20–32	EORTC	64%	47%	44	17%
Van der Wielen[12]	2007	3DCRT	69	68–78	34–39	SAQ	100%	62%	36	38%
Pinkawa[13]	2009	3DCRT	71	70.2–72	36–38	EPIC	81%	70%	16	11%
Fan[14]	2006	IMRT	71	72	40	Own	100%	10%	32	90%
McDonald[15]	2014	IMRT	68	67.6–70.2	36–38	SHIM	39%	19%	24	20%
Chen[16]	2017	IMRT	65	NS	NS	PCSI	100%	73%	24	27%
Hoffman[17]	2018	IMRT	67	75.6	42	Own	72%	48%	60	24%
Hoffman[17]	2018	IMRT	68	72	30	Own	78%	50%	60	28%
Friedland[18]	2009	SBRT	50	35	5	SHIM	100%	82%	24	18%
Chen[19]	2013	SBRT	69	35	5	SHIM	100%	79%	28	21%
Meier[20]	2013	SBRT	NS	40	5	EPIC	52%	36%	24	16%
Obayomi-Davies[21]	2013	SBRT	68	35–36.25	5	EPIC & SHIM	100%	54%	24	46%
Dess[22]	2017	SBRT	69	35–36.25	5	EPIC	100%	45%	60	55%
Fuller[23]	2018	SBRT	67	38	4	EPIC	58%	33%	60	25%
Ho[24]	2018	Proton	56	70–82	28–41	EPIC	90%	68%	60	22%
Chen[16]	2017	LDR	65	NS	NS	PCSI	100%	66%	24	34%
Valicenti[10]	2002	LDR	66	115	1	BSFI & SFI	75%	54%	12	21%
Feigenberg[25]	2005	LDR	NS	145	1	SAQ	73%	57%	12	16%
Nobes[26]	2008	LDR	61	145	1	IIEF	100%	62%	24	38%
Nobes[26]	2008	LDR	62	145	1	IIEF	100%	83%	24	17%
Solan[27]	2009	LDR	63	160	1	IIEF	100%	77%	26	23%
Huyghe[28]	2009	LDR	65	160.5	1	IIEF	90%	50%	36	40%
Taira[29]	2009	LDR	60	125 or 145	1	IIEF	100%	56%	84	44%
Pinkawa[30]	2009	LDR	68	145	1	EPIC	100%	81%	16	19%
Matsushima[31]	2013	LDR	NS	145–160	1	IIEF	100%	33%	12	67%
Frank[32]	2018	LDR	65	115–145	1	EPIC	68%	47%	48	21%
Ghadjar[33]	2014	HDR	63	38	4	Own	100%	75%	60	25%

RT radiotherapy, Gy/GyE gray or gray equivalent, *ED* erectile dysfunction, *3DCRT* 3D conformal radiotherapy, *LDR* low dose rate brachytherapy, *SBRT* stereotactic body radiotherapy, *BSFI* Brief Sexual Function Inventory, *SFI* sexual function index, *EORTC* European Organisation for Reasearch and Treatment of Cancer, *SAQ* Sexual Activity Questionnaire, *EPIC* Expanded Prostate Cancer Index Composite, *Own* self created, *SHIM* Sexual Health Inventory for Men, *PCSI* Prostate Cancer Symptom Indices, *IIEF* International Index of Erectile Function

questionnaires, 10 used the full questionnaire summary score. The remainder used one question from the validated questionnaire (most common was item 9 for EPIC).

Of the 2714 patients whose data was included in the analysis, 2326 patients (86%) reported normal erectile function before RT. At the time of follow-up measurement (median: 25 months, range: 12–84 months), 1559 patients (57%) reported having normal erectile function, with studies reporting between 6% and 69% of patients having developed ED during follow-up (Table 1). Figure 2 shows RT-induced ED as relates to study follow-up time and total dose. For patients receiving IMRT, the median increase in ED was 25%. For patients receiving 3DCRT, LDR BT and SBRT, the median increase in men reporting ED was 17%, 26%, 23%, and 23%, respectively. For the one proton study found, the incidence of ED increased 22% at a median follow-up of 5 years.

Univariate and multivariate analyses explored the role of treatment strategy and duration of follow-up on the development of RT-induced ED. In univariate analyses (Table 3) we found no significant differences between radiation types (p-values > 0.06). Multivariate analysis (Table 4) found a marginally statistically significant increased risk of developing ED with LDR relative to IMRT ($p = 0.05$). There was no significant difference noted between SBRT and 3DCRT, but the small sample size contributed to a large standard error ($p = 0.22$ and 0.10, respectively). This is thought to explain the non-significant result. The baseline likelihood of RT induced ED for a 66-year-old patient receiving IMRT with a follow-up time of 24 months and total dose of 72 Gy was 18%. This increased to 26% for a patient of similar age and follow-up receiving LDR ($p = 0.06$ univariate analysis, 0.05 multivariate analysis). For similar patients receiving SBRT, the risk of ED increased to 23%, but was insignificant ($p = 0.34$ univariate, $= 0.22$ multivariate). There was an increased risk of developing ED with higher radiation dose ($p < 0.0001$, Table 4). The odds of developing ED

Table 2 Summary of aggregate data by radiation modality.

Modality	Number of Studies	Number of Patients	Median FU (months)	Median Change in Erectile Function
3DCRT	4	316	32	17%
IMRT	5	283	42	26%
SBRT	6	739	25.8	23%
Proton	1	254	60	22%
LDR BT	11	1094	24	23%
HDR BT	1	28	60	25%
All Studies*	24	2714	24.9	24%

3DCRT 3D conformal radiotherapy, *IMRT* intensity modulated radiotherapy, *SBRT* stereotactic body radiotherapy, *LDR BT* low dose rate brachytherapy, *HDR BT* high dose rate brachytherapy.

*Some studies reported more than one modality.

Table 3 Univariate Analysis of Radiation Type.

Term	Log-odds	Odds	Standard error	z-value	p-value
Baseline	−1.1	0.33	0.14	−7.9	
3DCRT	0.01	1.01	0.19	0.054	0.96
LDR BT	0.28	1.32	0.15	1.9	0.061
SBRT	0.15	1.16	0.16	0.95	0.34

3DCRT 3D conformal radiotherapy, *LDR* low dose rate brachytherapy, *SBRT* stereotactic body radiotherapy.

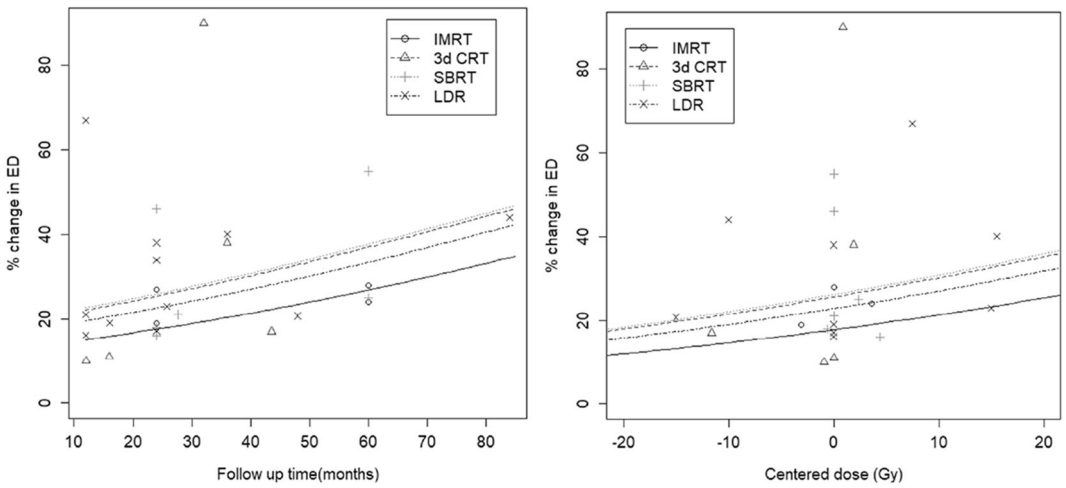

Fig. 2 Incidence of RT-induced ED over time as a function of: **a** follow-up time and **b** total radiation dose. Each symbol shows the reported percentage change in ED from beginning to end of each study. The type of RT used is indicated by different symbols. The black line shows the estimated effect of follow-up time and dose, respectively, in the baseline case (IMRT, 72 Gy and 24 months of follow-up) obtained from the multivariate logistic regression fitted to the data. For each modality, dose was centered at median dose for that modality.

Table 4 Multivariate logistic regression analysis of the factors contributing to RT-induced ED.

Term	Log Odds	Odds ratio	Std. Error	*z*-value	*p*-value
Baseline	−1.53	0.22	0.25	−6.08	
3DCRT	0.47	1.6	0.28	1.66	0.1
LDR BT	0.5	1.65	0.26	1.95	*0.05*
SBRT	0.31	1.36	0.26	1.22	0.22
Follow-up Length	0.02	1.02	0	5.69	**<0.0001**
Total dose	0.02	1.02	0.01	3.99	**0.0001**
With age as factor					
Baseline	−1.6	0.2	0.26	−6.2	
3DCRT	0.43	1.54	0.29	1.5	0.13
LDR BT	0.53	1.7	0.26	2	**0.042**
SBRT	0.46	1.58	0.26	1.8	0.079
Follow-up length	0.016	1.02	0.003	5.2	**<0.0001**
Total dose	0.02	1.02	0.0059	3.3	**0.001**
Age	0.024	1.02	0.013	1.8	0.078

Bold *p* values indicate statistical significance

The baseline refers to a 66 year old patient receiving IMRT with a follow-up time of 24 months and total dose of 72 Gy. For SBRT and LDR BT, dose was centered at median dose for that modality (35.6 and 145 Gy respectively). Note: a negative value indicates a protective relationship.

3DCRT 3D conformal radiotherapy, *LDR* low dose rate brachytherapy, *SBRT* stereotactic body radiotherapy.

increased by 2.2% for every 1 Gy increase in dose. Similarly there was a significant increase in ED with increased length of follow-up ($p = 0.0001$). The odds of developing ED increased by 1.5% for every 1 month increase in follow-up.

Median/mean age was included in a second multivariate analysis, finding similar relationships between follow-up time and total dose and RT induced ED but no significant association with age (Table 4, $p = 0.07$). Of note, raw age data was not available and so only the median or mean age as reported by each study was included.

Discussion

In this paper, we evaluated the effects of time and radiation modality on the development of ED in men who were potent prior to RT. Unsurprisingly, we found that there is a direct correlation between the incidence of ED and increasing radiation dose, as well as length of follow-up after irradiation. Importantly, our study documents that the rate of IMRT-induced ED is lower than that reported in older studies, and appears to be similar to the risk associated with LDR BT. We attribute this result to the high conformity of modern IMRT techniques. Comparison of SBRT with other techniques will require more studies with high quality ED data and sufficient follow-up.

Our findings suggest that use of modern highly conformal external beam techniques have successfully lowered the risk of ED compared to older studies – these note that the risk of developing ED in a man with normal erectile function prior to RT is 40–60%[34]. We hypothesize that the avoidance of erectile tissues, be it penile bulb, other nearby vascular structure, or neurovascular bundle, with very conformal RT relates to this risk reduction. This risk compares favorably with surgery. A prospective study comparing type of prostatectomy in the hands of experienced surgeons found that 68% and 74% of men reported ED two years after robotic vs open prostatectomy, respectively [34].

Our multivariate analysis notes a marginally significant trend where LDR BT is associated with a higher rates of ED development. We believe this is due to variability in the incidence of RT-induced ED for the LDR BT studies (range 16–67%) compared to IMRT (20–28% with one outlier of 90%). While more data over time is needed, we propose that the major finding here is the improvement in EBRT risk rather than the comparison between techniques.

There are several limitations to the data. First, in 2011, Alemozaffar et al. established the relationship between patient demographic data (patient-reported pre-treatment erectile function, age, prostate specific antigen levels, race/ethnicity, BMI), treatment modality, and predicted erectile function two years after prostate cancer treatment[35]. Given the nature of systematic reviews, patient populations across studies likely differ in ED risk factors. In particular, age was included in a secondary MVA analysis but with the caveat that raw age data was not available; thus sensitivity for differences by age is significantly reduced. Given the clear relationship between age and ED generally, we recommend that patients should be counseled on the impact age and various radiation treatment factors have one's long-term likelihood of developing of ED. We also note that co-morbidities and the use of sexual aids such as PDE-5 inhibitors, which can improve patient-reported sexual function, were rarely commented on in the studies reviewed. Comorbidities such as diabetes and peripheral vascular disease are common causes of ED which could confound the rates reported in these studies. Use of such sexual aids such as prescription medications, over the counter supplements, or physical aids could affect the reporting of erectile function at baseline and post-RT.

Secondly, studies included within this analysis likely varied in planning volume delineation, daily treatment set-up, and dosimetry to the penile bulb region, a structure that some have found to be predictive of ED[36]. Variation in timing of measurement is perhaps the greatest confounder in this effort. Between studies, median follow-up varied from

12 to 84 months. Because ΔED is likely dependent on time after the completion of RT, this could have affected the ΔED measured for study populations. Studies with shorter follow-up may therefore underestimate the incidence of RT induced ED, as it is likely progressive over time.

Finally, the method of ED measurement varied between studies. Currently, no consensus exists regarding the definition of erectile dysfunction, particularly amongst patients. The lack of standardization was reflected in our data, as 11 different instruments were utilized to evaluate changes in erectile function. Moreover, three studies utilized self-developed questionnaires rather than validated instruments to evaluate changes in RT-induced ED. This variability in ED measurement may affect the classification and quantification of erectile function as each patient-reported outcome measurement tool utilizes different scales and follow-up data points. Thus percent changes in erectile function across studies may not correspond well with one another. To negate some of this variability, we choose to measure the decline of erectile function within a study before comparing ΔED_i values across all studies included in the analysis.

Conclusions

This study summarizes and presents real-life experiences of patients receiving radiotherapy alone for previously untreated prostate cancer, and as such, offers insight into and support for common predictors of ED development. We note that RT-induced ED is still a common side effect of modern RT techniques, although at a somewhat lower frequency than has been reported in the past using older non-conformal EBRT. With modern treatment planning and delivery techniques, IMRT has a similar risk of ED development to LDR BT. This study not only highlights the progressive effect of RT on erectile tissues over time, but also a positive association between radiation dose and ED. Future research into RT-induced ED could be strengthened by careful planned reporting of erectile function. Up to 61% of patients in any individual study had ED prior to radiotherapy, thus we feel that attention to pre-existing ED is important in any analysis of treatment effect. By standardizing the methods used to classify and report ED, much more data could become available for future research. Moreover, further reduction in risk of RT-induced ED will be unlikely by technologic precision alone, but may require better understanding of the biologic mechanism of RT-induced ED. Additional information and understanding about how tissues surrounding the prostate respond to RT could possibly provide new approaches to protecting erectile functioning and providing significant improvements in QOL for millions of prostate cancer survivors in the United States and abroad.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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