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REVIEW

The Natural History of Erectile Dysfunction After Prostatic Radiotherapy: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Erectile dysfunction (ED) after treatment for prostate cancer with radiotherapy (RT) is well known, and pooled estimates of ED after RT will provide more accurate patient education.

Aim: To systematically evaluate the natural history of ED in men with previous erectile function after prostate RT and to determine clinical factors associated with ED.

Methods: We performed a review of the PubMed and Medline, Embase, Cochrane Library, and Web of Science databases in April 2016 according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. Identified reports included a measurement of ED before and after prostate RT. Two hundred seventy-eight abstracts were screened and 105 publications met the criteria for inclusion. Only men with known erectile function before RT were included in the analysis.

Outcome: ED after RT of the prostate.

Results: In total, 17,057 men underwent brachytherapy (65%), 8,166 men underwent external-beam RT (31%), and 1,046 men underwent both (4%). Seven common instruments were used to measure ED, including 23 different cutoffs for ED. The Sexual Health Inventory for Men (SHIM) was used in 31 studies (30%). Pooled estimates of SHIM-confirmed ED (score <10−17) suggested the prevalence of ED after RT is 34% of men (95% CI = 0.29−0.39) at 1 year and 57% (95% CI = 0.53−0.61) at 5.5 years. Compared with brachytherapy, studies of the two types of radiation increased the proportion of new-onset ED found by 12.3% of studies (95% CI = 2.3−22.4). For every 10% who were lost to follow-up, the proportion of ED reported increased by 2.3% (95% CI = 0.03−4.7).

Clinical Implications: ED is common regardless of RT modality and increases during each year of follow-up. Using the SHIM, ED is found in approximately 50% patients at 5 years.

Strengths and Limitations: The strengths of this systematic review include strict inclusion criteria of studies that measured baseline erectile function, no evidence for large effect size bias, and a large number of studies, which allow for modeling techniques. However, all data included in this analysis were observational, which leaves the possibility that residual confounding factors increase the rates of ED.

Conclusion: Definitions and measurements of ED after RT vary considerably in published series and could account for variability in the prevalence of reported ED. Loss to follow-up in studies could bias the results to overestimate ED. **Gaither TW, Awad MA, Osterberg EC, et al. The Natural History of Erectile Dysfunction After Prostatic Radiotherapy: A Systematic Review and Meta-Analysis. J Sex Med 2017;14:1071−1078.**

Key Words: Erectile Dysfunction; Radiation Therapy; Prostate Cancer; Sexual Health Inventory for Men (SHIM)

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INTRODUCTION

Prostate cancer is the second most common cause of cancer-related death in men.[1] Several options exist for the treatment of localized prostate cancer, including surgery, radiation therapy (RT), and active surveillance. RT treatment modalities include brachytherapy (BT), external-beam RT (EBRT), BT plus EBRT, or newer localized high-dose techniques.[2] Because patient survival is similar among the various treatments for prostate cancer, there is increased importance placed on understanding the side effects of each treatment.[3] Sexual function in particular is strongly affected by all prostate cancer treatments and is a major concern for patients.[4] Some evidence suggests that RT causes less sexual dysfunction, including erectile dysfunction (ED), compared with other treatments.[5,6]

The pathophysiology of ED after RT is complex and is believed to be due to endothelial cell damage to erectile tissues and damage to the arterial supply of the corpora cavernosa.[7,8] Rates of ED after RT vary, and meta-analyses have been limited because of the small number of studies and outdated RT techniques.[9] Pooled estimates of ED after RT will promote accurate patient counseling and shared decision making. Because overtreatment of prostate cancer is becoming increasingly recognized, the risks and benefits of the treatments offered must be appropriately scrutinized.[10] Our aim was to systematically evaluate the natural history of ED in men with previous erectile function after prostate RT and to determine the clinical factors associated with ED.

METHODS

Search Strategy

We searched the PubMed, Cochrane Library, Embase, and Web of Science databases in April 2016. The systematic literature search was conducted with the help of an expert information specialist (librarian). The complete search terms and search strategy are presented in Appendix A. The systematic review was registered with the PROSPERO database (registration number CRD42016038265), and all guidelines were followed according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement.[11]

Inclusion and Exclusion Criteria

Primary RT modalities, BT, EBRT, and BT plus EBRT, were all included from studies spanning 2000 to 2016. Included studies measured ED before and after RT with the same outcome metric. Randomized controlled trials (RCTs) were included if ED was measured before and after RT; however, only the control group was included in the analysis to minimize the effects of the intervention studied (ie, erectile aids). As such, all RCTs included in the study were cohort studies on RT. All studies included were original research of a unique cohort of patients. Separate studies of the same cohort of patients after RT were included if the follow-up times differed. All included studies were in the English language.

Studies of adjuvant or salvage radiotherapy for cancer recurrence were excluded. We excluded studies of surgery, cryotherapy, and high-intensity focused ultrasound therapy. Studies without baseline measurements of ED or studies that asked patients to self-recall erectile function before RT were excluded to avoid recall bias.[9] Figure 1 presents the flow of evidence acquisition and the application of our inclusion and exclusion criteria. We (T.W.G. and M.A.A.) used covidence.com to ensure a double-blinded review to determine included studies.

Data Collection and Data Extraction

We collected the total number of patients, radiation type and dosage, location of the study (United States and Canada, Europe, Asia, or Australia), study design (cohort vs RCT), follow-up time (years), and percentage of patients lost to follow-up. Clinical characteristics recorded included patient age, cancer pathology (Gleason score), percentage of patients on androgen deprivation therapy (ADT) before RT, and percentage of patients using erectile aids (medications and/or mechanical devices). We collected the median values of all continuous variables preferentially but recorded the mean if the median was not reported. We collected the type of ED measurement tool and which cutoff the investigators used to define ED after RT. ED measurement tools included erections sufficient for intercourse (yes or no), the International Index of Erectile Function and/or the Sexual Health Inventory for Men (SHIM), common terminology criteria for adverse events (CTCAE), Mount Sinai Erectile Function score (MSEF), the University of California—Los Angeles Prostate Cancer Index, and others, which included "potent with medications," spontaneous erections, satisfactory erections, or the Brief Sexual Function Inventory.[12–16]

Studies were grouped by the type of RT: BT, EBRT, or BT plus EBRT. If the study reported separate outcomes for ED by RT type, then we recorded these observations separately. If the study reported ED outcomes in a group of patients receiving different types of RT, then we coded these observations by which modality was most common. We recorded ED at all follow-up times reported in the study. If the biologically equivalent dose (BED) was not reported by the study, all doses were converted to the BED using an online calculator (http://eqd2.com/) or the referenced equation.[17]

Assessment of Publication Bias and Study Quality

We plotted the proportion of new-onset ED vs standard errors for graphic inspection of all studies (funnel plot; Appendix B). This analysis was repeated exclusively with patients included in the meta-analysis described below (Appendix C). We used the Egger test to determine whether small studies with large effect sizes biased our results. We did not find evidence of small-study bias ($P = .24$). All studies included had a prospective measurement of ED before and after RT. The use of various

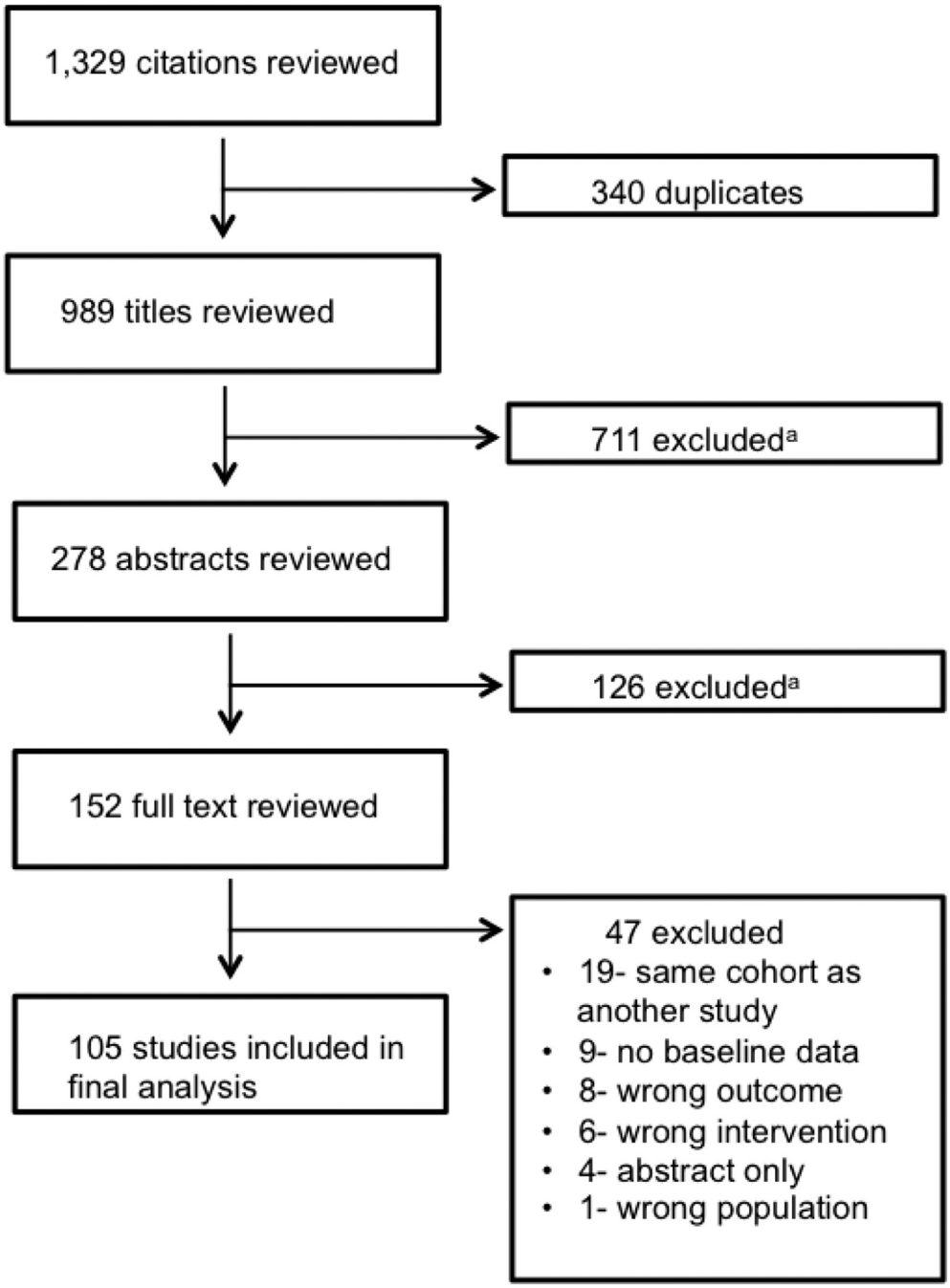

Figure 1. Flow of evidence and the application of our inclusion and exclusion criteria.

measurements of ED and confounding variables were accounted for by our regression analysis. Because studies differed in loss to follow-up (LTF), which ultimately can bias the proportion of ED in a given study, we used percent LTF as a surrogate for study quality.[18]

Data Synthesis and Analysis

Data analysis was conducted in STATA 13.0 (StataCorp, College Station, TX, USA). All tests were two-sided and any *P* values less than .05 were considered statistically significant. We used summary statistics to describe study and clinical characteristics of included studies.

Meta-Analysis

We combined estimates of new-onset ED (ie, percentage of patients who developed ED in the study). The proportion of patients with ED before RT was removed. Thus, the prevalence of ED at the time of RT for all studies was 0%. Because of such heterogeneity in ED measurement tools and ED cutoff points, we combined estimates only from studies that defined ED using

Table 1. Description of study characteristics included in the review (N = 103)*

Patients, N	26,269
Brachytherapy, n (%)	17,057 (65)
EBRT, n (%)	8,166 (31)
Brachytherapy + EBRT, n (%)	1,046 (4)
Year published, n (%)	
2000–2005	28 (27)
2006–2010	27 (26)
2011–2016	48 (47)
Location, n (%)	
USA and Canada	56 (54)
Europe	32 (31)
Asia	10 (10)
Australia	5 (5)
Design, n (%)	
Cohort	95 (92)
RCT	8 (8)
Follow-up study (y), median (IQR)	3 (2–5)
Patients lost to follow-up (%), median (IQR)	25 (14–41)
Patient age (y), median (IQR)	66 (65–68)
Gleason score, median (IQR)	6 (5.8–6)
Androgen deprivation therapy (%), median (IQR)	10 (0–33)
Erectile aids (%), median (IQR)	17 (0–39)
BED (Gy), median (IQR)	172 (130–178)

BED = biologically equivalent dose; EBRT = external-beam radiation therapy; IQR = interquartile range; RCT = randomized controlled trial.
*Two studies reported on the same cohort; this table presents 103 unique cohorts.

Table 2. Erectile dysfunction measurements and definitions of all included studies (N = 103)

	Studies (N = 103)*	Definition
Erection sufficient for intercourse	36 (35%)	Yes or no (33 studies)
		Always or almost always (2 studies)
		Change from baseline (1 study)
IIEF-5 and SHIM	31 (30%)	<22 (3 studies)
		<17 (6 studies)
		<10–13 (15 studies)
		>2 change in score (1 study)
		Score only (4 studies)
		Unclear (2 studies)
CTCAE (version 2-4)	11 (11%)	Grade ≥ I (1 study)
		Grade ≥ II (8 studies)
		Grade ≥ III (2 studies)
MSEF	7 (8%)	≥2 (6 studies)
		≥3 (1 study)
UCLA-PCI	6 (6%)	<67 (1 study)
		Change from baseline (3 studies)
		Score only (2 studies)
Get and maintain erection	6 (6%)	Yes or no (5 studies)
		Score (1 study)
Other	6 (6%)	
Potent with medications	2	Yes or no
Spontaneous erections	1	Yes or no
BSFI-EF	1	Score
Satisfactory erection	1	Less than satisfactory

BSFI-EF = Brief Sexual Function Inventory—Erectile Function; CTCAE = common terminology criteria for adverse events; IIEF-5 = International Index of Erectile Function; MSEF = Mount Sinai Erectile Function score; SHIM = Sexual Health Inventory for Men; UCLA-PCI = University of California—Los Angeles Prostate Cancer Index.
*Two studies reported on the same cohort; this table presents the 103 unique cohorts.

the SHIM.[12] The cutoff scores for defining ED in this analysis ranged from 10 to 17. Cutoffs outside this range were deemed too different to combine estimates and were excluded from this analysis. This was the most common, objective, and validated measure used and thus was selected for pooled estimation.[12] We performed meta-analysis of proportions stratified by follow-up time using a random-effects model.[19] The follow-up times that were used to combine estimates were determined by the quartiles of follow-up times in the studies (1, 2, 3, and 5.5 years). Because of the limited number of studies using a common measure, we did not stratify by RT modality. We performed a sensitivity analysis by including only those studies with a cutoff score of 22 to determine the effect of a more conservative definition of ED at 1 year.

Meta-Regression

We used generalized estimating equations to model all new-onset ED proportions reported in studies. In the model, we included RT modality, measurement tool, patient age, percentage of patients on ADT, BED, follow-up time, and LTF. We did not adjust for erectile aids, because this was not reported consistently in publications. We repeated this regression model using meta-regression to ensure that study weights were accounted for. Studies that did not dichotomize ED were excluded from this analysis (n = 11) because the proportion of new-onset ED was not interpretable.

RESULTS

Description of Studies

One hundred five studies met the inclusion criteria. A list of all studies is presented in Appendix D. Two studies were of the same cohort but with different follow-up times; thus, there were 103 unique patient cohorts. In total, 17,057 men underwent BT (65%), 8,166 men underwent EBRT (31%), and 1,046 men

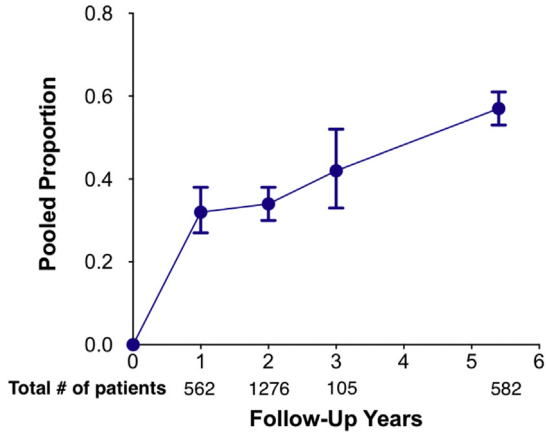

Figure 2. Pooled proportion of erectile dysfunction after radiotherapy confirmed by the Sexual Health Inventory for Men using cutoffs from 10 to 17. Figure 2 is available in color at www.jsm.jsexmed.org.

underwent BT plus EBRT (4%). Most studies were cohort studies (95 [92%]), and the median follow-up time per study was 3 years (interquartile range [IQR] = 2–5). The median percentage of patients on ADT before RT was 10.1% (IQR = 0–33). The median Gleason score in all studies was 6 (IQR = 5.8–6). Table 1 presents a description of all study characteristics collected. The median percentage of patients using an erectile aid was 17% (IQR = 0–39). However, the use of erectile aids was reported in only 43 studies (41%).

Seven common instruments were used to measure ED, with 23 different cutoffs for ED. Table 2 lists all ED instruments reported and the cutoff values for ED definition. The most common measurement was whether one's erections were sufficient for intercourse (yes or no) in 36 studies (35%). The SHIM was used in 31 studies (30%).

Meta-Analysis of Natural History of ED After RT

Twenty-one studies met the inclusion criteria. Pooled estimates of SHIM-confirmed ED (score <10–17) suggested the prevalence of ED after RT is 34% of men (95% CI = 0.29–0.39) at 1 year, 39% (95% CI = 0.33–0.44) at 2 years, 44% (95% CI = 0.34–0.53) at 3 years, and 57% (95% CI = 0.53–0.61) at 5.5 years. Figure 2 presents the results of these combined estimates by follow-up time. The specific studies included in this analysis are presented in Appendix E. The median age of patients in this analysis was 66 years (IQR = 62–68). The median percentage of patients on ADT was 0% (IQR = 0–17.5). The median LTF in these studies was 21% (IQR = 11–31). The estimated 1-year prevalence of ED for those with a SHIM cutoff score lower than 22 was 48% (95% CI = 0.31–0.66).

Meta-Regression of All Estimates

Table 3 presents generalized estimating equation and meta-regression models for the outcome of proportion of new-onset ED in a study. There were no differences in the proportion of new-onset ED between BT and EBRT. Compared with BT, studies of the two types of radiation increased the proportion of new-onset ED found by 12.3% of studies (95% CI = 2.3–22.4). When comparing ED measurement tools, the CTCAE estimates decreased the proportion of new-onset ED by 10.8% (95% CI = 0.4–21.2). Median age reported, percentage of patients on ADT, and BED did not statistically increase the proportion of new-onset ED in studies. Increasing LTF was associated with an increase of the proportion of men with ED. For every 10% who were lost to follow-up, the proportion of ED reported increased by 2.3% (95% CI = 0.03–4.7). We observed no changes in statistical interpretation between the generalized estimating equation model and the meta-regression model.

DISCUSSION

We present a systematic review and meta-analysis of RT and ED in a large group of studies from 2000 to 2016. Using a SHIM cutoff score of 10 to 17, new-onset ED was found in approximately half the patients at 5 years after RT. Receiving EBRT and BT is associated with a higher incidence of post-radiation ED. In our meta-regression, we found no significant differences in reported ED after BT vs EBRT. No standard tool for ED exists, and the type of measurement tool can yield significantly different reports of ED. LTF in observational studies of ED after RT can increase the reported prevalence of ED.

There were numerous ED measurement tools with a wide range of ED cutoff points. Studies of ED rates after localized prostate cancer treatment do not consistently assess erectile function.[20] Most studies assessed erectile function from a single question asking whether the patient had erections sufficient for intercourse. Since this time, many studies have provided evidence for the reliability and validity of measurement tools to assess ED.[13,14,21–23] In our regression analysis, we found no differences among the various tools and the proportion of ED. This corresponds to previous evidence that the MSEF score and the SHIM are highly correlated.[14] However, compared with the definition of erections sufficient for intercourse, the CTCAE reported lower rates of ED. This is could be due to the fact that the CTCAE defines ED by whether erectile aids are needed.[24] Thus, other measurement tools might be measuring other aspects of sexual function that go beyond erectile aid usage, which are affected by RT. Other factors such as sexual desire, medical and physical morbidities, and partner availability were not reviewed in this analysis and will present future challenges to measurement.[25]

The pooled proportion of ED after RT in our review shows that roughly one third of patients will present with ED at 1 year and one half will present with ED at 5 years. However, these results must be interpreted with caution. The SHIM cutoff points that defined ED at follow-up ranged from 10 to 17 and the exact range of SHIM scores at baseline is unknown. Thus, the range of potency at baseline is defined at 11 to 25, which is a large range of

Table 3. Regression and meta-regression of new-onset erectile dysfunction (proportion) after prostate radiotherapy

	GEE model			Meta-regression		
Study characteristic	β Coefficient	95% CI	*P* value	β Coefficient	95% CI	*P* value
Radiation Type						
Brachytherapy	0.0	reference	—	0.0	reference	
EBRT	−3.4	−12.2 to 5.4	.46	−3.4	−14.8 to 7.9	.55
Both	12.3	2.3–22.4	.02	13.4	2.4–24.3	.02
Measurement						
ESFI	0.0	reference	—	0.0	reference	
IIEF-5 or SHIM	−1.3	−9.0 to 6.5	.75	−0.4	−9.3 to 8.4	.92
CTCAE (version 2-4)	−10.8	−21.2 to −0.4	.04	−10.8	−21.3 to −0.3	.04
MSEF	2.2	−9.8 to 14.1	.72	2.7	−10.1 to 15.5	.81
UCLA-PCI	1.1	−9.8 to 11.9	.85	1.8	−13.1 to 16.7	.81
Get and maintain erection	−3.0	−12.6 to 6.7	.55	−2.5	−16.1 to 11.0	.71
Other*	−9.2	−19.7 to 1.2	.08	−8.6	−22.9 to 5.7	.24
Median age	−0.3	−1.6 to 1.0	.67	−0.2	−1.5 to 1.0	.69
Percentage on ADT	−0.04	−0.2 to 0.1	.50	−0.1	−0.2 to 0.2	.38
BED does (Gy)	0.00	−0.2 to 0.2	.91	−0.01	−0.2 to 0.2	.87
Follow-up (y)	0.3	−1.2 to 1.8	.65	0.3	−1.2 to 1.8	.69
Percentage of LTF	0.2	0.01–0.5	.05	0.2	0.03–0.5	.03

ADT = androgen deprivation therapy; BED = biologically equivalent dose; CTCAE = common terminology criteria for adverse events; EBRT = external-beam radiation therapy; ESFI = erections sufficient for intercourse; GEE = generalized estimating equation; IIEF-5 = International Index of Erectile Function; LTF = loss to follow-up; MSEF = Mount Sinai Erectile Function score; SHIM = Sexual Health Inventory for Men; UCLA-PCI = University of California–Los Angeles Prostate Cancer Index.
*Other includes potent with medications, spontaneous erections, satisfactory erections, or Brief Sexual Function Inventory.

"normal" erectile function. The generalizability of these results must be considered in relation to the patients who were included in these studies. The median age ranged from 60 to at least 70; and the percentage of patients on ADT was small (1.4% of patients; Appendix E), potentially minimizing confounding effects of ADT on ED. As a result, our estimates are slightly lower than those of two large studies of erectile function after prostate cancer therapy.[26,27] After applying the more conservative definition of ED (SHIM score <22), the prevalence of ED increased and might be another reason for this lower estimate.

Results from our regression models show that receiving EBRT plus BT is associated with increased ED. We did not find any significant differences in ED prevalence between BT and EBRT monotherapy. The impact of RT on various anatomic structures (ie, penile bulb) has been studied, and increased radiation to vascular structures can increase the likelihood of ED.[28,29] The dose of RT was not associated with ED. This most likely reflects the trend of increasing doses of RT to more localized structures during the past 10 years and the fact that high-dose RT is associated with less toxicity compared with low-dose RT.[30,31] Therefore, ED might be most dependent on the number of structures involved. Doses to specific structures were not collected in this review and are not commonly reported.

Specific issues associated with epidemiologic studies of ED, such as recall bias and measurement bias, have been identified.[32] Because the measurement of ED is not dependent on the type of radiation received, most of this bias is toward the null. However, differential LTF can be difficult to avoid in all longitudinal studies and can bias toward a spurious effect. We show that, on average, the proportion of ED increases by approximately 2% in studies for every 10% of patients who are lost to follow-up. This suggests that patients who experience ED might be more likely to follow-up in studies compared with patients who are not experiencing these side effects. Such selection bias can be corrected for and might be a strategy researchers could use in the future. Most studies did not have a control cohort, and some proportion of ED could be a result of time alone.[6]

The strengths of this systematic review include strict inclusion criteria of studies that measured baseline erectile function, no evidence for large effect size bias, and a large number of studies, which allow for modeling techniques. However, all data included in this analysis were observational, including the control arms of RCTs, which leaves the possibility that residual confounding factors increase the rates of ED. We did not have a control group of normal erectile function. We confronted the possibility of confounding by controlling for median age, percentage of patients on ADT, RT dose, follow-up time, and loss to follow-up. However, the median values collected for these variables were inconsistently reported and do not represent the study population perfectly. Mismeasurement of these confounding variables might account for the lack of association between such variables (ie, age and ADT) and ED after RT, because measurement error would bias the effect estimates toward the null. The use of erectile aids was not reported consistently and not

included in this analysis. Although our random-effects models control for heterogeneity in the sample, we could not determine the exact causes of this heterogeneity. There is potential mismatch of radiation type assigned in our analysis, because some studies did not report ED outcomes separately between these groups. Radiation techniques such as targeted radiosurgery, proton beam radiation, and intensity-modulated radiation therapy were not included in our study so we could focus on the most common methods selected by men diagnosed with localized prostate cancer.[33] As with all systematic reviews, publication bias might overestimate an effect, although visual inspection of our funnel plots suggests otherwise. The meta-analysis included studies of BT and EBRT, and although the meta-regression did not show significant differences in ED rates between these treatment modalities, the pooled estimates must be interpreted as such. Despite these limitations, clinicians can refer to our data to provide anticipatory guidance before and after RT for prostate cancer. Consensus in measurement and definition of ED also might allow clinicians and patients to commonly interpret study results.

CONCLUSIONS

Definitions and measurements of ED after RT vary considerably in published series and could account for variability in the prevalence of reported ED. Nevertheless, ED is common regardless of RT modality and increases during each year of follow-up. BT plus EBRT is associated with increased ED, whereas the prevalence of ED did not differ between BT and EBRT monotherapies. Using the SHIM, ED is found in approximately 50% patients at 5 years. LTF in studies could bias the results to overestimate ED.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jsxm.2017.07.010.