Title

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Radiation-induced Fistulas in Patients With Prior Pelvic Radiotherapy for Prostate Cancer: A Systematic Review and Meta-analysis

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OBJECTIVE To systematically aggregate and summarize existing data on fistula prevalence among patients with a history of pelvic radiotherapy for prostate cancer.

MATERIALS AND METHODS We queried PubMed, Embase, and Web of Science on October 7, 2020 for peer-reviewed publications pertaining to radiation-induced fistulas in the pelvis. For meta-analysis, we used the random-effects model. We used the I^2 statistic to quantify heterogeneity and the Newcastle-Ottawa Scale to assess risk of bias.

RESULTS Our final meta-analysis included 6 cohort studies with a total of 7665 patients exposed to pelvic radiotherapy between 1967 and 2013. Median follow-up time was 35.5 months (IQR 33.5-57.5). Pooled prevalence of radiation-induced fistula across all 6 cohort studies was 0.2% (95% CI: 0.1-0.4, I^2 = 0.000%, $P < .608$). In subgroup analysis, we did not detect significant heterogeneity in fistula prevalence in patients who were re-irradiated (0.3%, 95% CI: 0.1-0.4; $P = .762$) or patients on concurrent chemotherapy (0.4%, 95% CI: -0.3 -1.2; $P = .664$) compared to those receiving their first course of radiotherapy alone. No randomized controlled trials met inclusion criteria due to ambiguous and inconsistent reporting language for fistula occurrence.

CONCLUSION There is limited published literature reporting fistula as an adverse event of prostate cancer radiotherapy, especially in the medium and long-term period. Patients undergoing pelvic radiotherapy for prostate cancer appear at low short-term risk for developing fistulas. Adverse event reporting in randomized controlled trials merits greater granularity where fistulas should be reported with specificity rather than aggregating into broad categories of genitourinary or gastrointestinal adverse events. UROLOGY 00: 1–6, 2023. © 2023 Elsevier Inc.

Fistula formation is one of the most morbid complications that patients with pelvic malignancies can experience after undergoing pelvic radiotherapy. Radiation-induced fistulas can involve multiple pelvic organ systems including rectal (eg, rectourethral or rectovesical), enterovesical, and enterocutaneous.[1-5] Depending on the grade and organs involved, radiation-induced fistulas and their repair can have profound impacts on quality of life and impair activities of daily living.[6,7] Fistulas can also lead to infections and urosepsis. Given the serious morbidity that radiation-induced fistulas can cause patients, it is important to understand the risk of developing fistula after receiving radiation therapy. This is crucial for patient counseling and continued optimization of radiation regimens.

Unfortunately, little is known about the prevalence of fistulas in patients treated with pelvic radiotherapy. A review on pelvic complications after prostate cancer radiotherapy found that fistula formation is a rare complication, albeit there is "need for higher-quality studies" to provide accurate estimates of the risk of fistula after radiotherapy.[8] Separately, a review on the urological complications of pelvic radiotherapy reported that vesicovaginal fistulas and rectovesical fistulas might be the most common types of fistulas in women and men, respectively, although the authors' results were limited by the "paucity of published literature" and inadequate follow-up in the existing literature.[9]

[#] *These authors contributed equally to this work*

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Table 1. Characteristics of N = 6 cohort studies Included in meta-analysis

Median population size per study, (IQR)	415.5 (82-2051)
Total pooled population	7665
Median follow up time, months (IQR)	35.5 (33.5-57.5)
Median age, years (IQR)	66 (65-66)
Types of radiotherapy, No. (% out of 6 studies)	
≥2 types of radiotherapy*	4 (66.7)
EBRT	2 (33.3)
Total fistulas reported in all studies, No. (crude % out of 7665 patients in pooled population)	22 (0.29)

Individual study characteristics				
First author	Year published	No. patients	Type(s) of radiotherapy	No. patients with fistulae
Abadir	1984	93	Brachytherapy +	1
Perez	1994	738	EBRT	2
Dinges	1998	82	Interstitial + EBRT	2
Stone	2013	2051	Brachytherapy +/- EBRT	4
Rutenberg	2016	11	EBRT	1
Leong	2016	4690	Brachytherpay +/- previous EBRT	12

* In these studies, not all patients received the same type of radiotherapy (eg, some received external beam radiotherapy, while others received brachytherapy or even combined modality).

The purpose of this systematic review and meta-analysis is to aggregate and summarize existing data from cohort studies and randomized controlled trials (RCTs) reporting on fistula prevalence among patients with prostate cancer who have undergone pelvic radiotherapy.

MATERIALS AND METHODS

To find relevant articles, we searched PubMed, Web of Science, and Embase databases. We searched broadly across these main concepts: radiation therapy, fistula, and pelvis. We added multiple synonyms for each concept to build searches that were sensitive and would capture all important articles, and we used both index terms (Mesh, Emtree) and keywords in our searches (Supplemental Table). We conducted our initial search on October 7, 2020, and included all eligible studies found to that date. Due to a low yield of RCT data from our initial search strategy, we appended our search on July 2, 2021 in search of phase III RCTs that had been published in the last 10 years. Our searches of the gray literature included individually searching the references of articles included for data extraction and reviewing conference abstracts found in Embase. The full search strategies for each database are included in the Supplemental Table.

To be included in our systematic review and meta-analysis, studies must: (1) be a cohort study or a phase III RCT; (2) be on the topic of radiotherapy for prostate malignancy; (3) report specific toxicity associated with radiotherapy, including but not limited to fistula. At least 2 reviewers (MS, NH, BN, JH, WS, KDL) independently and in duplicate screened the abstracts and then full texts of the citations identified by our search strategy to assess for eligibility. They used a standardized form to record reasons for exclusion. Disagreements between reviewers were resolved by senior investigator (GA). At least 2 reviewers then abstracted the following data independently and in duplicates: study design, demographics, and clinical characteristics of the patient population, and quantitative data on our main outcome of interest which is radiation-induced fistula.

We conducted the meta-analysis using the random-effects model to account for between-study heterogeneity. We used I^2 statistic to assess heterogeneity between studies and the Newcastle-Ottawa Scale to assess risk of bias. PRISMA guidelines[10] were followed, and our protocol was registered *a priori* on PROSPERO. All analyses were conducted in Stata version 17.0 (StataCorp, College Station, TX).

RESULTS

Our final meta-analysis included 6 cohort studies with a total of 7665 patients exposed to pelvic radiotherapy between 1967 and 2013.[5,11-15] Study selection flow chart is presented in Figure 1. Median patient age was 66 years and median follow-up time was 35.5 months (Table 1). Of the 6 cohort studies we included, 4 (66.7%) reported outcomes of patients undergoing combination radiotherapy with 2 or more modalities. In these studies, not all patients received the same type of radiotherapy (eg, some received external beam radiotherapy, while others received brachytherapy or even combined modality). Two (33.3%) of the cohort studies reported EBRT-related toxicity. We chose not to report dose information due to substantial within-study heterogeneity, which made it impossible to determine which dose was received by patients who developed fistula.

Pooled prevalence of radiation induced fistula across all 6 cohort studies was 0.2% (95% CI: 0.1-0.4) and ranged between 0.2% and 9.1%. There was no significant heterogeneity among studies (I^2 = 0.000%, P < .608, Fig. 2). Fistula prevalence was slightly higher in studies that included patients who were re-irradiated (0.3%, 95% CI: 0.1-0.4) compared to studies that only included first-time radiotherapy recipients (0.2%, 95% CI: 0.1-0.4) but this was not statistically significant (P = .762, Fig. 3). Likewise, fistula prevalence was slightly higher among patients undergoing radiotherapy with concurrent chemotherapy (0.4%, 95% CI: −0.3 to 1.2) compared to those receiving radiotherapy alone (0.3%, 95% CI: 0.1-0.1) (P = .664; Fig. 3). When stratifying the pooled prevalence of fistula by type of radiotherapy by comparing the pooled prevalence among studies that used ERBT only vs studies in which ≥2 modalities were used, there was no significant heterogeneity between treatment groups (I^2 = 0.00%, P = 0.855) suggesting that the risk of fistula may be the same across all types of radiotherapy.

None of the RCTs met inclusion criteria due to ambiguous reporting language: they did not use the word "fistula" but instead used broader language to report toxicities (eg, "grade 3 toxicity"), making it impossible to determine the prevalence of fistula in those trials.

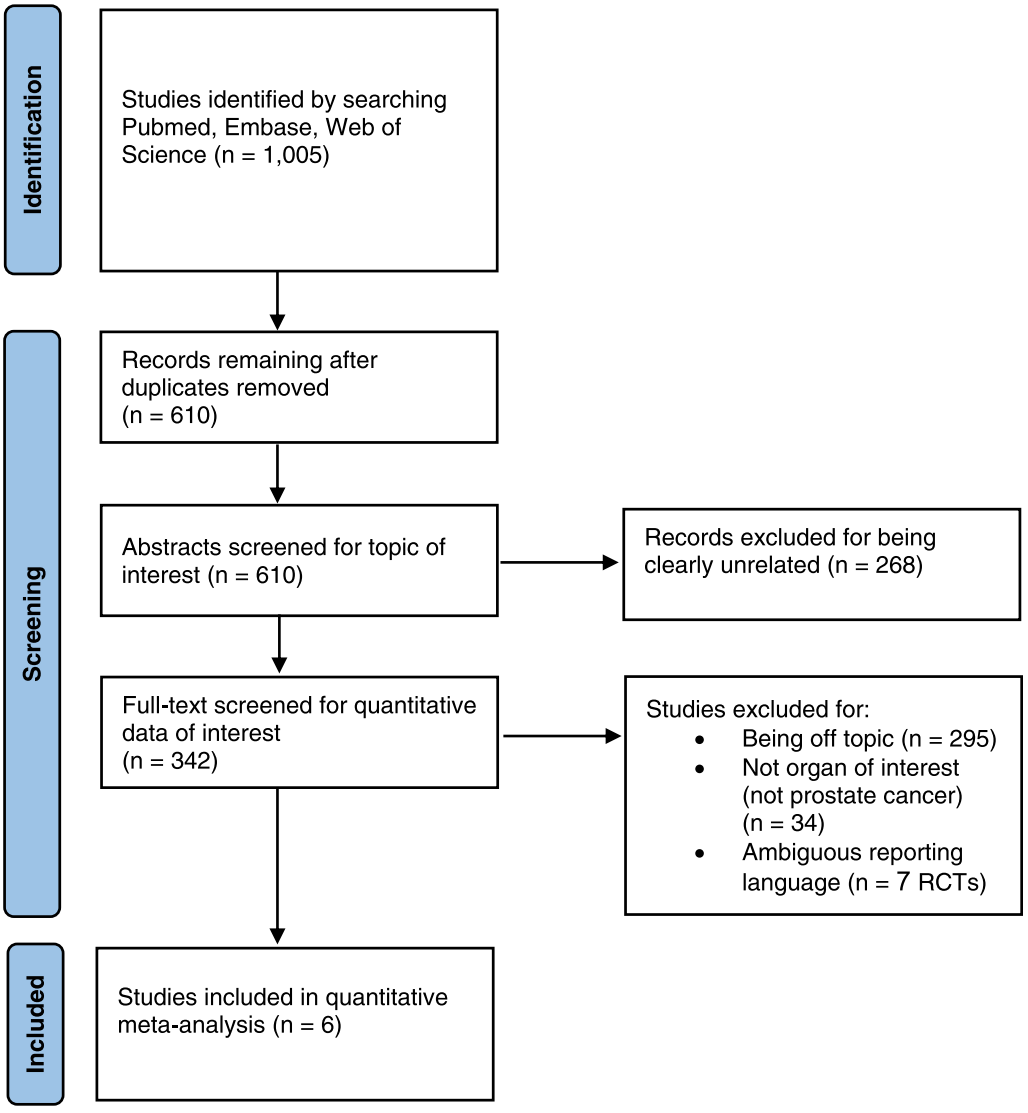

Figure 1. Flow chart for selection of studies to include in meta-analysis (Color version available online.)

DISCUSSION

Our data align with existing literature which concluded that radiation-induced fistula is a rare yet poorly studied complication and that there is a "need for higher-quality studies assessing these outcomes and their management."[8,9] While the existing data demonstrates some evidence of a dose-dependent relationship for risk of radiation-induced fistula,[16] our study was unable to report dose-dependent toxicity, and the literature is mixed on this.[17,18] Regarding the type of radiotherapy, our study found no association between type of radiotherapy and fistula risk (I^2 = 0.00%, P = .855), yet there is some evidence in the literature that combined modality radiotherapy such as EBRT plus brachytherapy may confer increased risk of fistula.[19] The mixed and conflicting results in the literature reflect a need for future studies that are designed to describe the risk of radiation-induced fistula with substratified analysis based on patients' demographic and clinical characteristics, and with sufficient follow up time to capture the occurrence of fistula.

Our results are subject to several limitations and biases. No RCTs met inclusion criteria due to ambiguous and inconsistent reporting language for our outcome of interest (ie, fistula). For example, rather than specifically reporting whether patients developed fistula after undergoing radiotherapy, the studies would use vocabulary such as "grade 3 genitourinary toxicity" which precludes us from knowing if the study population, and what percentage of them, experienced fistula. None of the 7 RCTs that we reviewed contained the word "fistula" yet our assumption is that there was a nonzero prevalence of fistula across those 7 trials. As a result of omitting these RCTs, the results of our present study were based solely on an aggregate of cohort studies, most of which were single-center

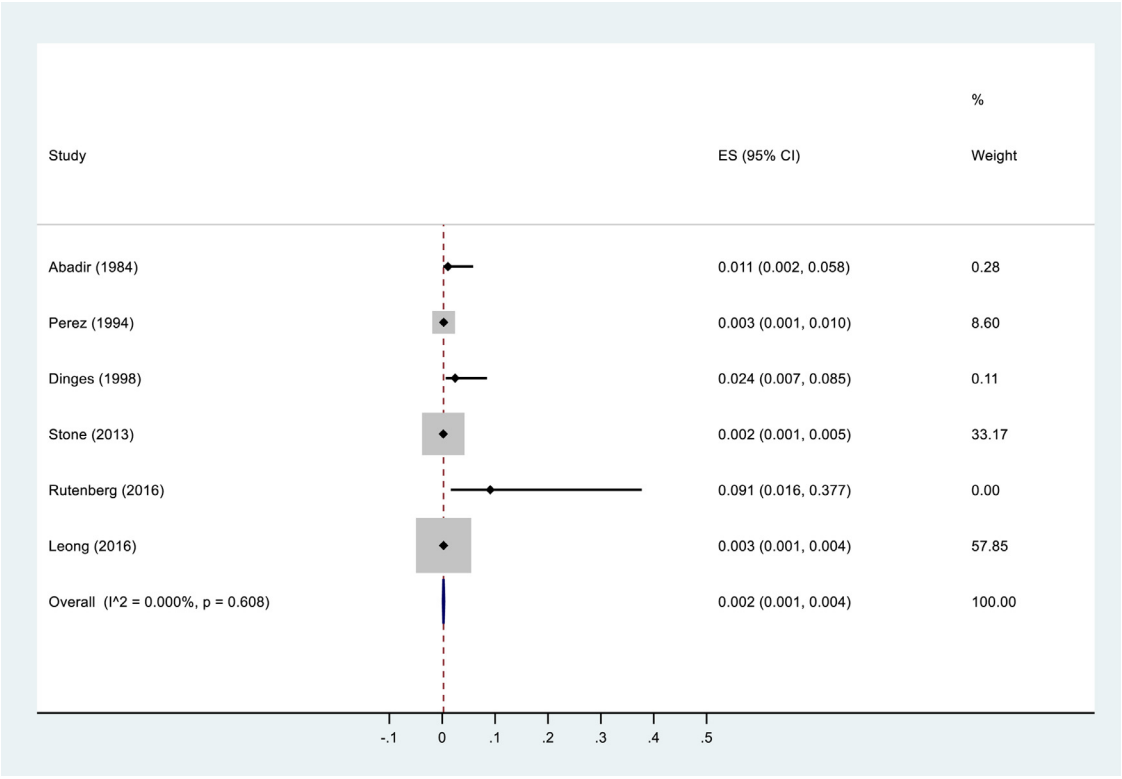

Figure 2. Pooled prevalence of fistula across 6 cohort studies (total n = 7665 patients) (Color version available online.)

studies with unqualifiable variation in radiation regimens. These excluded RCTs were investigating the effects of radiotherapy on oncologic outcomes, and thus were not designed to answer our specific research question on the risk of fistula development after pelvic radiation.

Another potential source of bias is our search strategy (Supplemental Table) and whether or not the word "fistula" is included as a search term. For example, our initial search strategy included the word "fistula" and this yielded the 6 cohort studies with 7665 patients and a pooled fistula prevalence of 0.2%. In contrast, when we searched for RCTs we did not include the word "fistula" and this yielded 7 trials with zero confirmed cases of fistula out of 2549 total patients. On the other hand, the short follow up times in our included studies would likely underestimate the true prevalence of fistula. Similarly, we believe the 0 confirmed cases of fistula across our 7 RCTs must be an underestimation of the true prevalence, and this is due to inconsistent reporting language which may lead to unreported fistulas. Finally, we include studies dating back to the *1970s* recognizing that radiotherapy regimens have significantly changed, and new technologies have emerged to prevent unwanted radiation (eg, SpaceOAR).[20] These changes have an unknown effect on fistula rate and there was no correlation with publication year.

Despite these limitations, we believe our results are a useful starting point for estimating the risk of developing a pelvic fistula after pelvic radiotherapy, as well as illuminating clinical factors that may increase risk of fistula such as reradiation or concurrent chemotherapy. Of note, both reradiation and chemotherapy could be surrogates for more advanced or aggressive pelvic malignancy which may be the unmeasured risk factor increasing fistula risk. Moreover, by highlighting the inconsistent reporting language across the existing RCTs on this topic—and the lack of studies that are dedicated to investigating the risk of fistula—we hope the results of our systematic review and meta-analysis will inspire future authors of future RCTs to report specific adverse effects rather than reporting the grade of toxicity. Knowledge of specific adverse effects would help clinicians counsel their patients on the risks of undergoing radiotherapy.

CONCLUSION

Patients undergoing radiotherapy for prostate malignancy are at low risk for developing fistulas in the short-term. Given the significant heterogeneity in the existing literature on radiation-induced fistula, the lack of RCTs reporting the risk of radiation-induced fistula, and the short follow-up time of the existing studies, there is need for cohort studies and RCTs specifically designed to address the currently ambiguous question about long term risk of developing fistula for patients undergoing radiotherapy for prostate cancer.

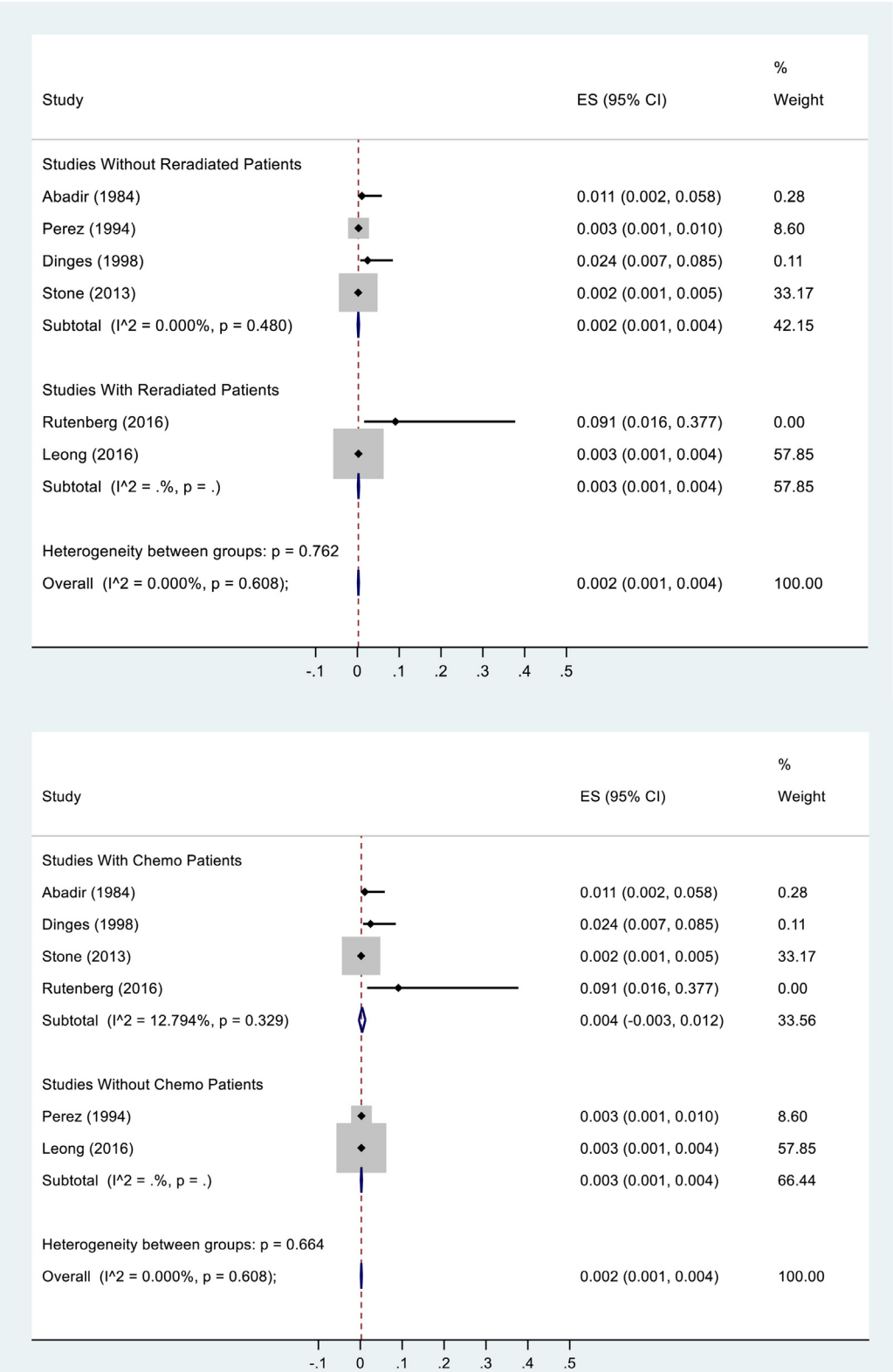

Figure 3. Pooled Prevalence of fistula across 6 cohort studies separating studies with (n = 4701) and without (n = 2964) re-irradiated patients (upper panel) and studies with (n = 2237) and without (n = 5428) patients that were on concurrent chemotherapy (lower panel) (Color version available online.)

DATA AVAILABILITY STATEMENT

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

CONSENT FOR PUBLICATION

All authors provide consent for publication.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2023.03.015.

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