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Female erectile tissues and sexual dysfunction after pelvic radiotherapy: a scoping review

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Abstract

Introduction: Sexual function is a vital aspect of human health and is recognized as a critical component of cancer survivorship. Understanding and evaluating the impacts of radiotherapy on female sexual function requires precise knowledge of organs involved in sexual function and the relationship between radiotherapy exposure and sexual tissue function. Although substantial evidence exists describing the impact of radiotherapy on male erectile tissues and related clinical sexual outcomes, there is very little research in this area in females. The lack of biomedical data in female patients makes it difficult to design studies aimed at optimizing sexual function post radiotherapy treatment for female pelvic malignancies.

Aims: This scoping review identifies and categorizes current research on the impacts of radiotherapy on normal female erectile tissues including damage to normal functioning, clinical outcomes of radiation-related female erectile tissue damage, and techniques to spare erectile tissues or therapies to treat such damage.

Methods: An evaluation of the evidence was performed and a summary of findings was generated per PRISMA-ScR guidelines. Manuscripts were included in the review that involved normal female erectile tissues and radiotherapy side effects.

Results: Results show that little scientific investigation into the impacts of radiotherapy on female erectile tissues has been performed.

Conclusion: Collaborative scientific investigations by clinical, basic and behavioral scientists in oncology and radiotherapy are needed to generate radiobiologic and clinical evidence to advance prospective evaluation, prevention and mitigation strategies that may improve sexual outcomes in female patients.

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Keywords

radiotherapy; sexual dysfunction; cancer; survivorship; female sexual toxicity

Introduction

Sexual function is a vital aspect of human health and is recognized as a critical component of cancer survivorship[1]. Sexual dysfunction—including difficulties with interest, comfort, arousal or orgasm—is prevalent among women receiving radiotherapy for pelvic malignancies and can cause significant distress[2–14]. Maintaining the capacity for pleasurable sexual activity after cancer therapy can be fundamental to quality of life[1], yet there are few effective preventative and mitigating strategies for female* patients[1, 8, 15, 16].

The female erectile tissues—herein described as the bulboclitoris[17] or the organ comprised of the clitoris and vestibular bulbs[18, 19]—compose the anatomic basis for female sexual arousal and orgasm[20, 21]. While the impact of radiotherapy on organs such as the vagina or ovaries, vital to sexual and reproductive function in female patients, has been studied in detail, the impact of radiotherapy on erectile tissues is lacking despite the fact that they are often included in the radiotherapy fields for pelvic malignancies and are injured by this treatment[2, 3, 7–11, 22]. Conversely, the impacts of radiotherapy on male erectile tissues and associated neurovasculature[23], methods and biomarkers measuring radiation-related damage to these tissues[23, 24], and the related impacts of radiotherapy on sexual function outcomes is well established[23–26].

Evaluating the impact of radiotherapy on the function of the female erectile tissues requires synthesizing existing evidence to inform and design studies of this emerging research area. A comprehensive review on this subject has yet to be performed.

To address this deficiency, this scoping review aims to identify and report current evidence on the effect of radiotherapy on female erectile tissues and related sexual toxicities. The goal of this review is to comprehensively address the primary research questions including: what is the impact of radiotherapy on female erectile tissues; what are the toxicities and associated clinical outcomes secondary to radiotherapy effects on female erectile tissues; what techniques, methods, or biomarkers are used to assess the impact of radiotherapy on female erectile tissues; finally, what techniques or therapies are currently used to treat radiation-related damage to female erectile tissues.

Materials and Methods

We performed a scoping review per the PRISMA Extension for Scoping Reviews (PRISMA-ScR)[27] and the Joanna Briggs Institute[28] to examine the extent, range, and nature of available research and identify research gaps[29]. A scoping review provides a rigorous comprehensive, systematic approach to synthesize current heterogeneous literature to identify gaps in knowledge and provide an effective summary for practitioners and guide researchers. This review focuses on female patients who received radiotherapy treatment for pelvic malignancies (including external beam radiation therapy, proton therapy and

interstitial as well as intracavitary brachytherapy). Primary studies that investigated any effect of radiotherapy on the function normal female erectile tissues were identified.

With the guidance of a research librarian, search terms were generated and preliminary searches were used to refine the search strategy. Table 1 shows the PICOS (Population, Intervention, Comparison, Outcome, Study design) framework used to guide the initial inclusion/exclusion of research reports. Our systematic protocol was registered in the Open Science Framework database (https://osf.io/tyfa8/). We then performed a comprehensive search of electronic bibliographic databases, including in PubMed/MEDLINE using MeSH and Title/Abstract terms. We also conducted a hand search of the reference list of included studies.

The preliminary search strategy included combinations of specific terms for the female erectile tissues [(clitor* or vestibular bulb* or bulbs of the vestibule or bulb of the vestibule) or (female and (corpora spongios* or corpus spongios* or corpus cavernos* or corpora cavernos* or pudendal or orgasm or erectile))], and terms for radiotherapy: radiation or irradiat* or radiotherap* or proton* or brachy*. All full-text studies that were published between 1971 and September 2020, in English, in peer-reviewed journals, and addressed the review question were included.

Two reviewers (D.M. and J.K.) independently screened all titles/abstracts retrieved by the search strategy to identify articles according to the inclusion and exclusion criteria. In case of disagreement, a third independent reviewer was consulted (J.B.). Tiebreak was required in four instances with an inter-rater reliability of 0.90 (95% confidence interval: 0.82, 0.94). Studies were excluded from full-text review when they discussed non-cancer topics or included primary malignancy of the tissues of interest. Studies were also excluded if they exclusively discussed outcomes unrelated to radiotherapy (“non-radiotherapy outcomes”; e.g. surgical outcomes alone without any discussion of radiotherapy outcomes), or reported solely on outcomes unrelated to the function of the erectile tissues (“other morbidities”; e.g. diarrhea).

After initial screening, full text was obtained for further assessment. A standardized data extraction form was used, including authors, year of publication, title, article type, population, aims, methodology, outcomes, and important results. Quality of quantitative publications was assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies[30] and a numerical analysis regarding the extent, nature and distribution of reports was provided along with a narrative synthesis to describe characteristics of relevant reports. Formal risk of bias assessment was not applicable for this scoping review, consistent with Arksey and O’Malley’s framework[29] and Joanna Briggs Institute methodological guidance for Scoping Reviews[28].

Results

Of the 55 identified articles (Figure 1), 41 were excluded because they did not meet study inclusion criteria during the initial review process. The reasons they did not meet inclusion criteria were the following: patients with malignancy of the organ (vulva or erectile tissues),

n=25; non-radiotherapy outcomes, n=7; non-cancer topics, n=5; and, other morbidities, n=4. Of the 13 remaining articles, 10 were excluded after full-text review. The reasons for exclusion of articles were the following: non-radiotherapy outcomes, n=6; and, other morbidities, n=4.

Three articles were included in the final review and narrative synthesis (Table 2): one guideline and two non-randomized studies on intervention effects. Articles were published between 2005 and 2015. Both quantitative studies were of good quality but included small sample sizes for pilot data collection and thus had limited scope and generalizability. One study by Pietrangeli et al.[31] included a direct assessment of patients receiving surgery and radiotherapy on nerve function of the erectile tissues, however this study included a small number (n=10) of patients who had received chemoradiotherapy and their outcomes were not reported separately for males and females. The quality of this study was poor given the limited pre-post participation rate, small sample size and lack of sample size justification, single post-treatment assessment not completed on all participants, and lack of controlling for confounding variables. The second study by Schroder et al.[32] evaluated an intervention to improve sexual outcomes using validated sexual outcome measures and physical exam but was limited to a pilot cohort of 13 female patients.

Discussion

This systematic scoping review of the radiation oncology literature revealed that consideration of the role of the erectile tissues in female sexual function related to radiotherapy has been limited to three manuscripts[31–33]. Only the important guideline by Brooks et al.[33] for contouring male and female genital structures includes portions of the bulboclitoris (only the glans and body of the clitoris) in the external genitalia contours. However, even here the erectile tissues are combined with cutaneous/subcutaneous tissue and fat, which serve a distinct function from erectile tissue. Given that tissue tolerance for radiation is organ-specific, the erectile tissues likely have a different tolerance for radiation based on unique organ structure and function, requiring high level evidence to test this hypothesis. Further, the female genital structures delineated in external genitalia contours are protected to reduce dermatologic toxicity, rather than to protect the sexual function of the bulboclitoris.

In an important and unique departure from other radiation toxicity papers, Schroder et al.[32] discuss a clitoral therapy device to improve sexual pleasure outcomes in female patients treated for cervical cancer, though again focus primarily on the clitoral glans and body in their anatomic approach. Finally, Pietrangeli et al.[31] discuss nerve stimulation of the sexual organs, including the bulboclitoris, in a cohort that included 24 female surgical patients with rectal cancer, although attention to female patients in the subset receiving chemoradiotherapy (n=10) was not provided. Outside this review, the general toxicity literature on sexual outcomes after pelvic radiotherapy rarely discusses arousal and orgasm except for in the realm of vaginal sex[34–38].

In addition to our limited findings, the minimal evidence base for understanding the impacts of radiotherapy on female erectile tissues is exemplified by the lack of systematic or

scoping reviews on this topic. Previous articles have discussed sexual dysfunction caused by cancer care, but not the direct effects of radiotherapy. This is in sharp contrast to the broad evidence base for the impacts of pelvic radiotherapy on male erectile tissues. In this patient population, erectile tissue complications after radiotherapy such as erectile function and ejaculation have been studied in detail[23, 24, 39], included as endpoints in clinical trials[23–25], and have been used to determine who will benefit from advanced techonologies[40]. Importantly, these anatomic complications are included as fundamental discussion points in shared decision making with patients – especially since some patients are willing to forgo longevity to avoid sexual dysfunction[41]. Our findings demonstrate that the function of and damage to female erectile tissues in pelvic cancer patients receiving radiotherapy remains an under-represented scientific domain. Addressing this scarcity of data has a broad and invaluable potential impact as the experience of sexual pleasure is essential to human sexuality across the lifespan, including for cancer survivors, and should receive equitable consideration for females as in males[1, 26]. Collaborative scientific investigations by clinical, basic and behavioral scientists in oncology and radiotherapy are needed to generate radiobiologic and clinical evidence to advance prospective evaluation, prevention and mitigation strategies that may improve sexual outcomes in female patients. We provide a summary of our recommendations for future research and the potential impact and significance of these investigations in Table 3.

Limitations of this review include the inclusion of articles written only in English. In addition, our search criteria included only full-text articles and does not include research that may have been presented at conferences and is yet to be published in a peer-reviewed journal. In addition, since our review only focused on female erectile tissues, sexual dysfunction in female cancers as a whole is not addressed.

Our next steps are guided by our primary finding of the omission of female erectile tissues from investigations of radiation toxicities, which precludes the development of robust interventions to prevent, mitigate and treat sexual toxicities related to cancer treatment. The evidence synthesized by this review and the knowledge gap revealed, justifies and informs future foundational studies necessary to understand the effect of radiotherapy on normal female erectile tissues and the resultant impact on clinical outcomes.

Conclusion

The lack of research on the impact of radiotherapy on female erectile tissues is a problem that needs to be addressed to provide comprehensive evidence-based survivorship care in sexual health for female patients. Further investigation is essential to develop effective interventions to prevent and mitigate treatment-related toxicity due to radiotherapy damage to the female erectile tissues.

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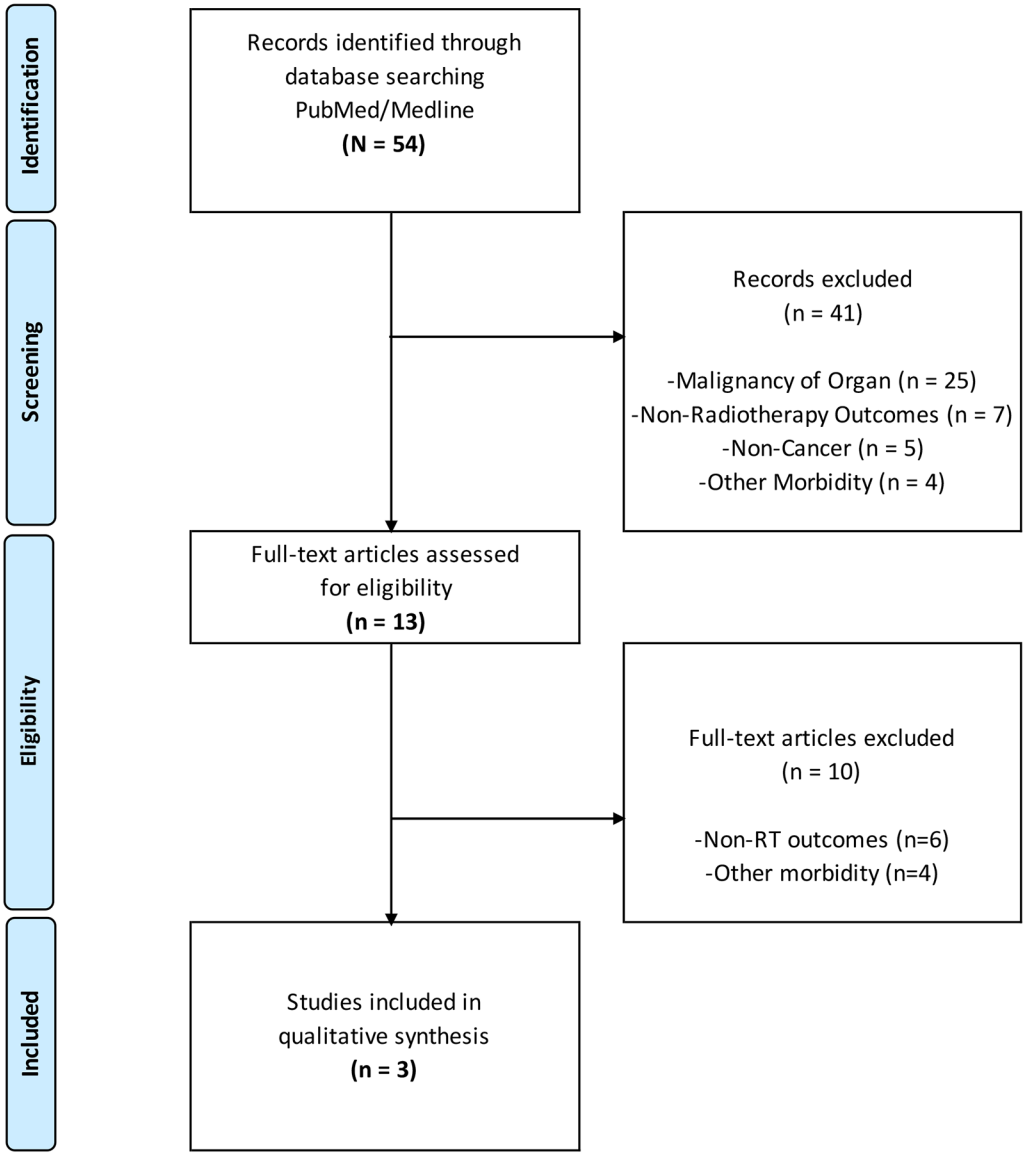

Figure 1. PRISMA Flow Diagram

Abbreviations: RT, radiotherapy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1.

Population, Intervention, Control, Outcome, Study Design (PICOS) inclusion criteria

Population:	Female patients with pelvic malignancies
Intervention:	Pelvic radiotherapy in the preoperative, postoperative or definitive settings
Control:	Comparators were optional
Outcomes:	Post-radiotherapy sexual function related to erectile tissues
Study design:	All guidelines, reviews, and retrospective, prospective, and basic scientific studies

Table 2.

Study characteristics of articles related to pelvic radiotherapy damage to female erectile tissues

Authors	Year	Title	Article Type	Population	Aims	Methodology	Outcome Measures	Important Results	Quality
Brooks C, Hansen VN, Riddell A, Harris VA, Tait DM.	2015	Proposed genitalia contouring guidelines in anal cancer intensity-modulated radiotherapy.	Guideline	N/A	Description of a genitalia contouring atlas for anal canal carcinoma radiotherapy	Image review, institutional multi-disciplinary team consensus, and literature review	N/A	Contouring guidance for genitalia; genitalia constraints and dose received -- Model dose constraints: V20Gy<50%; V30Gy<35%; V40Gy<5%; Max<48–50Gy. Median Mean Dose: 23.7Gy (22.1–29.1Gy)	N/A
Pietrangeli A, Pugliese P, Perrone M, Sperduti I, Cosimelli M, Jandolo B.	2009	Sexual dysfunction following surgery for rectal cancer - a clinical and neurophysiological study.	Non-Randomized Study on Intervention Effects	Total N=57 patients with rectal cancer. N=24 females and N=10 patients also treated with chemoradiation. Males and females in this subgroup were not analyzed independently. Includes a subset analysis of those receiving chemo-radiotherapy.	To evaluate the effect of total mesorectal excision with nerve-sparing on sexual function including innervation of erectile tissues	Structured interview and neuro-psychological tests	Sexual function, sacral reflex, evoked potentials and sympathetic skin responses	59.6% reported sexual impotence overall. increased sacral reflex and sympathetic skin responses and 10% reporting sexual function abnormality in 3 year time frame.	Poor
Schroder M, Mell LK, Hurteau JA, Collins YC, Rotmensch J, Waggoner SE, Yamada SD, Small W Jr, Mundt AJ.	2005	Clitoral therapy device for treatment of sexual dysfunction in irradiated cervical cancer patients.	Non-Randomized Study on Intervention Effects	13 female patients with cervical cancer treated with radiotherapy	Evaluation of the efficacy of a clitoral therapy device in reducing radiation-related sexual dysfunction	Pilot cohort study	Difference from baseline to 3 months on the Female Sexual Function Index, Derogatis Interview for Sexual Functioning, Dyadic Adjustment Scalè	At 3 months, the median Female Sexual Function Index total score increased from 17 to 29.4 (p <0.001); the median Derogatis Interview for Sexual Functioning total raw score increased from 46 to 95 (p <0.001); and, gynecologic examinations revealed improved mucosal color and moisture, vaginal elasticity and decreased bleeding and ulceration.	Good

Table 3.

Recommendations for Future Research

Research Priorities	Research Impact and Significance
BASIC, RADIOBIOLOGIC and TRANSLATIONAL RESEARCH	
Elucidate the impacts of radiation on female erectile tissues and their neurovasculature • molecular and cellular mechanisms of radiation tissue damage and repair • mechanistic interactions with hormones and other cancer directed therapies • genomic and immunologic basis for radiation response in these tissues	Will enable the development of precision interventions to prevent or mitigate radiation damage to female erectile tissues, modify individual susceptibility, and manage toxicity progression.
Identify erectile-tissue specific dosimetric predictors of organ damage and subsequent dysfunction	Precise dose-volume indices can be identified for use in treatment planning below which the risk of clinically-relevant radiation damage to the erectile tissues and resulting difficulty with orgasm and arousal remains low. Build evidence base for advanced technologies such as proton therapy or MRI-guided radiotherapy.
Identify objective quantitative imaging biomarker indices of radiation damage	Objective biomarkers are needed to address multidimensional sexual outcomes, and may improve performance of toxicity probability models. Developing reliable biomarkers of radiation effects in erectile tissues can also be used to improve treatment optimization and inform early interventions.
Improve anatomic knowledge of the structure and function of the bulboclitoris organ	Accelerate development of anatomy-directed interventions (e.g. suction devices or topical therapies) by incorporating a detailed understanding of anatomic structure, location and function.
CLINICAL RESEARCH	
Reclassify sexual quality of life measures using precise understanding of the underlying organ dysfunction that incorporates erectile tissues	Ensure radiation damage and organ dysfunction are aligned, recognizing the impacts of damage to female erectile tissues on sexual quality of life.
Revise toxicity criteria and diagnosis codes to include erectile tissue organ dysfunction as a genital or anatomic basis of toxicity.	Allow systematic measurement of arousal/orgasm outcomes related to organ damage to be measured in clinical trials and other studies.
Develop reproducible standardized anatomic contours of erectile tissues for females.	Harmonize data across studies and institutions to advance research objectives. Inclusion of the bulboclitoris in radiotherapy planning will reveal the role that bulboclitoris damage plays in altering orgasm and arousal functions after radiotherapy.
Determine variability of radiation dose delivered to the bulboclitoris and feasibility of avoidance without compromising tumor control or other important toxicity outcomes.	Bulboclitoris normal tissue complication modeling will generate the first radiation planning indices that can be employed clinically to maintain of a low rate of bulboclitoris-related complications without compromising cancer outcomes. Such modeling is necessary to identify the benefit of advanced technologies or to allow for shared decision making–especially since some patients are willing to trade longevity to avoid sexual dysfunction. Will enable prospective trials such as cooperative group anatomy-sparing phase II trials and/or integration into other therapeutic trials.
Elucidate the precise relationship of radiation dose, erectile tissue toxicity, and sexual outcomes such as arousal, orgasm, and dyspareunia.	Provide an evidence base for clinical discussions about late effects of radiotherapy that can be expanded to include female sexual pleasure.
Elucidate the relationship between erectile tissue function and multimodality cancer care (surgery, endocrine therapies, ovarian failure), biopsychosocial aspects of sexuality, and social determinants of health	Improve the performance of toxicity models using multidimensional predictors sexual outcomes. Identify needs for multidisciplinary team-based approaches to managing sexual outcomes in cancer survivorship.
Evaluate equitable distribution of radiotherapy resources related to sexual outcomes.	Improve equity in the investment of research and development funding and generate evidence to support equitable distribution of advanced technologies.

Research Priorities	Research Impact and Significance
EDUCATION	
Develop education interventions for radiation oncology clinicians about the structure, function and importance of bulboclitoris anatomy to female sexual outcomes.	Empower clinicians to incorporate female sexual pleasure and relevant anatomy into clinical decision-making.
Develop patient-provider educational interventions on incorporating erectile tissue toxicity into discussions about treatment-related toxicity and exploration of shared decision-making.	Normalize female sexual pleasure as an important aspect of sexuality in cancer survivorship and re-orient discussions about sexual outcomes to prioritize maintenance of sexual pleasure in addition to vaginal health.