

RADIATION-INDUCED VAGINAL STENOSIS FOLLOWING CA CERVIX TREATMENT - SYSTEMATIC REVIEW

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Abstract

Background: Cervical cancer remains a significant global health challenge, and radiation therapy plays a crucial role in its management. However, pelvic radiation therapy can lead to long-term complications such as radiation-induced vaginal stenosis (VS). Despite its clinical significance, there is a lack of comprehensive literature reviews that specifically focus on radiation-induced VS in the context of cervical cancer treatment. **Objectives:** This systematic review aimed to provide a thorough analysis of the incidence, predictors, and management strategies of radiation-induced vaginal stenosis after cervical cancer treatment. **Materials and Methods:** A systematic search was conducted using major scientific databases, including PubMed, Scopus, and Web of Science, until April 2024. Studies investigating the development of vaginal stenosis caused by radiation therapy in women with cervical cancer were included. A narrative synthesis approach was employed to analyse the study characteristics, methodologies, and major findings. **Results:** The synthesis of the findings from the eight selected studies provided significant insights. Incidence of vaginal stenosis in patients treated for cervical cancer. The rates of mild, moderate, and severe stenosis reached 97.5%, 60.7%, and 7.4%, respectively, three years after post-brachytherapy. Various factors, such as pallor reaction grade, adherence to dose constraints, and patient age, were identified as significant predictors of VS. Management strategies, including patient counselling, adherence to dose constraints, vaginal dilator use, and imaging modalities, have been highlighted as effective approaches to mitigate the development and severity of VS. **Conclusion:** This systematic review highlights the significance of early detection and specific treatment for the management of radiation-induced vaginal stenosis in patients receiving treatment for cervical cancer.

INTRODUCTION

Cervical cancer is a persistent and significant global health concern. In 2020, there were 604,000 new cases and 341,000 deaths worldwide.^[1] Although screening and treatment strategies have improved, radiation therapy is still crucial in managing locally advanced forms of the disease. It can be used as a primary treatment or as an adjunctive measure after surgery. However, pelvic radiation can unintentionally harm nearby healthy tissues, causing long-term complications. Despite the potential side effects, radiation therapy is an essential treatment option for patients with cervical cancer, helping to

control the disease and increase survival rates.^[2] But, it can lead to adverse effects, with vaginal stenosis being a significant concern.

Radiation-induced vaginal stenosis is a known complication of pelvic radiation therapy and is often used to treat gynaecological cancers such as cervical cancer. The severity and duration of vaginal stenosis can vary among patients, and it is often accompanied by other side effects such as vaginal fibrosis, atrophy, and shortening. The symptoms include dyspareunia, vaginal dryness, and sexual dysfunction. This condition not only causes physical discomfort but also has a profound impact on the

affected individual's quality of life, sexual gratification, and emotional well-being.^[3]

The incidence of radiation-induced vaginal stenosis varies depending on treatment elements, patients, and tumour factors. The development of VS depends on various factors such as the site of disease, radiation treatment modality and dose, coexisting chemotherapy, patient age, and radiosensitivity of the tissues. The incidence of radiation-induced VS was primarily based on small patient groups and retrospective data. It also depends on the methods used for evaluating VS and the grading systems employed.^[4]

Despite its clinical significance, there is a scarcity of comprehensive literature reviews that specifically delve into radiation-induced vaginal stenosis in the realm of cervical cancer management. The existing body of literature primarily comprises disjointed studies characterised by disparate methodologies and incongruous findings. Consequently, it is necessary to systematically combine the available data to gain deeper insight into the true consequences of this complication and provide guidance for clinical efforts.

The principal objective of this systematic review was to conduct a thorough analysis of the incidence, predictors, and management of radiation-induced vaginal stenosis after cervical cancer treatment.

MATERIALS AND METHODS

Literature Search Strategy

A systematic and exhaustive search was conducted across major scientific databases, including PubMed, Scopus, and Web of Science, to identify relevant studies related to the development of vaginal stenosis caused by radiation therapy in women with cervical cancer. The search covered studies published until April 2024. The search strategy included variations of keywords such as "radiation-induced vaginal stenosis", "cervical cancer treatment", and other related terms. Boolean operators (AND, OR) were used to refine the search and capture the intersection of these terms.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria.

- Studies involving adult patients (≥ 18 years) diagnosed with cervical cancer and treated with pelvic radiation therapy.
- Peer-reviewed articles published in English until April 2024.
- Randomised controlled trials (RCTs), cohort studies, case-control studies, and observational studies have reported original data.

Studies were excluded if they were as follows

- Published in languages other than English.
- Case reports, reviews, or conference abstracts.
- Studies involving non-cervical cancer cohorts.
- Dissertations, theses, and conference abstracts were excluded from the study.

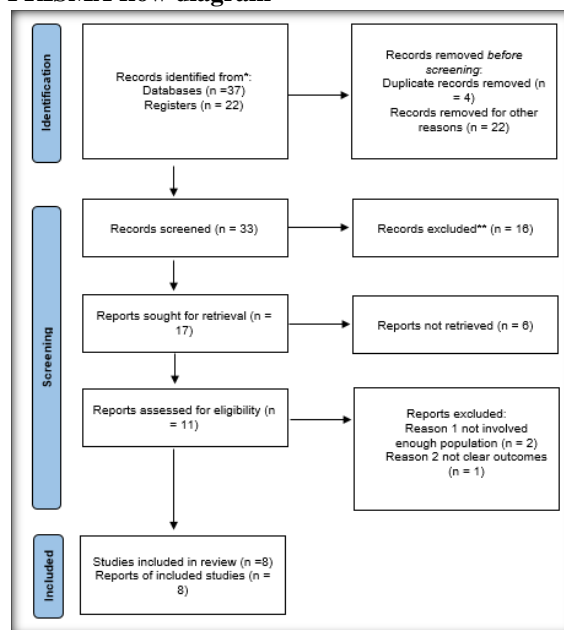
Synthesis of Findings

Data synthesis involves a narrative synthesis of the relevant study characteristics, methodologies utilised, and major findings of radiation-induced vaginal stenosis following cervical cancer treatment. Given the expected diversity in study designs, a qualitative approach was employed to highlight the distinctive contributions of each study to a comprehensive understanding of this complication.

Ethical Considerations

As this review was based on an analysis of previously published studies, ethical approval was not applicable. All the included studies adhered to ethical standards, as outlined in their respective publications.

PRISMA flow diagram



RESULTS

A systematic review of these eight studies revealed numerous significant discoveries concerning the incidence, predictors, and treatment of vaginal stenosis (VS) after different therapies for cervical and associated malignancies.

A systematic review of the selected studies revealed significant insights into the incidence, predictors, and management strategies for VS following the treatment of cervical and related cancers. Notably, the study by Yoshida et al., involving 57 patients, underscored a high incidence of late VS, with rates of mild, moderate, and severe stenosis reaching 97.5%, 60.7%, and 7.4%, respectively, three years after brachytherapy. Brachytherapy is a type of internal radiation therapy in which seeds, ribbons, or capsules that contain a radiation source are placed in the body, in, or near the tumour. This study emphasized the predictive value of pallor reaction grade at six months posttreatment for developing moderate to severe stenosis.^[5,6]

Similarly, Bruner et al. The incidence of vaginal stenosis in 90 patients treated for either cervical carcinoma (n = 42) or endometrial carcinoma (n = 48) with standard doses of intracavitary radiation from 1989 to 1992.^[7] Son et al. found that sparing vaginal volume to a low dose during pelvic radiation therapy for rectal or anal cancer significantly reduced the incidence of severe VS, with adherence to dose constraints playing a crucial role,^[8] Law et al. highlighted the effectiveness of vaginal dilator (VD) use in minimizing VS; however, adherence to recommended VD use was poor, indicating the need for improved strategies.^[9]

Regarding pelvic radiotherapy, Kirchheiner et al.'s analysis of the EMBRACE study showed that while severe vaginal morbidity was low, mild to moderate symptoms persisted, necessitating continued attention.^[10] Additionally, Brand et al.'s retrospective chart review identified advanced age (>50 years) as a significant predisposing factor for developing VS following pelvic and vaginal radiotherapy.^[11] Furthermore, Williamson et al. demonstrated the utility of CT imaging in detecting radiation-induced VS, with menopausal status and smoking history influencing dimensional changes.^[12] Lastly, Miccò et al. proposed diffusion-weighted MRI as a valuable tool for predicting CRT-induced VS in locally advanced cervical cancer patients, highlighting its potential for early prevention and management strategies.^[13]

Various strategies have been identified to mitigate the incidence and severity of radiation-induced vaginal stenosis following cervical cancer treatment. Yoshida et al.'s findings emphasize the significance of patient counselling and preventive interventions

in managing late VS following high-dose-rate brachytherapy.^[5] Son et al. suggest that adherence to dose constraints, particularly sparing vaginal volume to a low dose during pelvic radiation therapy, could significantly reduce the risk of severe VS.^[8] Additionally, Law et al. highlight the effectiveness of vaginal dilator (VD) use in minimizing VS, albeit with poor adherence observed at 12 months, indicating the need for strategies to improve compliance and determine optimal VD use frequency and duration.^[9]

Furthermore, the EMBRACE study by Kirchheiner et al. underscores the importance of monitoring and addressing mild to moderate vaginal symptoms persisting after treatment, despite relatively low rates of severe vaginal morbidity.^[10] Brand et al.'s retrospective chart review emphasizes the need for monitoring and management of VS, particularly in older patients undergoing pelvic and vaginal radiotherapy, where age over 50 years was identified as a significant predisposing factor.^[11] Lastly, Miccò et al.'s study suggests diffusion-weighted MRI as a valuable tool for early prevention and management strategies of VS in locally advanced cervical cancer patients after chemoradiation therapy, potentially enabling timely interventions to mitigate VS development (Table 1).^[13]

RT, radiation therapy; VS, vaginal stenosis; VD, vaginal dilator; IGABT, image-guided adaptive brachytherapy; CTCAE, Common Terminology Criteria for Adverse Events; CRT, chemoradiation therapy; LACC, locally advanced cervical cancer; DW-MRI, diffusion-weighted magnetic resonance imaging; TV, tumour volume.

Table 1: Characteristics and key findings of included studies

Study Authors	Study Design	Participants (n)	Key findings
Yoshida et al.	Prospective cohort	57	<ul style="list-style-type: none"> Over half of the patients (97.5%) developed mild vaginal stenosis within the first year after high-dose-rate brachytherapy. Moderate-to-severe stenosis rates increased over time. Pallor reaction grade 2-3 at six months post-treatment predicted moderate-to-severe stenosis three years later. Higher pallor reaction grades at six months were associated with a significantly higher risk of developing grade ≥ 2 vaginal stenosis.⁵
Bruner et al.	Prospective cohort	90	<ul style="list-style-type: none"> Vaginal stenosis was observed in 90 patients treated with intracavitary radiation therapy for cervical or endometrial carcinoma. After treatment, slightly more women reported sexual activity, but 22% experienced decreased frequency and 37% reported decreased satisfaction.⁷
Son et al.	Prospective cohort	54	<ul style="list-style-type: none"> Sparing the vaginal volume to a low dose during pelvic radiation therapy significantly reduces the incidence of severe VS. Compliance with the dose constraints is crucial. A generalised equivalent uniform dose (gEUD) below 35 Gy and a mean vaginal dose under 43 Gy were associated with decreased severe VS incidence. Higher mean doses were correlated with more negative changes in dilator size. Patients with low compliance (<40%) are more prone to toxicity.⁸
Law et al.	Prospective cohort	109	<ul style="list-style-type: none"> VD use effectively minimised VS; however,

			<p>adherence at 12 months was poor (42%).</p> <ul style="list-style-type: none"> • Most participants maintained their pre-RT VD size at 12 months, with factors such as disease type, younger age, and increased adherence at six months influencing size maintenance or return. • Strategies to improve adherence and determine optimal frequency and duration of VD use are warranted.⁹
Kirchheiner et al.	Prospective cohort	588	<ul style="list-style-type: none"> • Severe vaginal morbidity (grade ≥ 3) 2 years post-treatment was low (3.6%) in patients with locally advanced cervical cancer treated with IGABT. • Mild-to-moderate symptoms (grade ≥ 1, 89%; grade ≥ 2, 29%) persisted, with stenosis being the most frequent symptom followed by vaginal dryness. • IGABT was relatively safe in terms of severe vaginal morbidity, but attention to mild to moderate symptoms is required for continued management.¹⁰
Brand et al.	Retrospective cohort	188	<ul style="list-style-type: none"> • Vaginal stenosis occurs in 38% of patients with cervical carcinoma treated with pelvic and/or vaginal radiotherapy. • 27% experienced grade 1 toxicity and 11% grade 2 toxicity. • Stenosis typically occurs within the first year after treatment, with a mean onset of 9.6 months. • Age over 50 years was the only prognostic factor associated with increased stenosis risk, highlighting the need for monitoring and management in older patients undergoing radiotherapy.¹¹
Williamson et al.	Retrospective cohort	104	<ul style="list-style-type: none"> • A significant reduction in vaginal width at the apex and mid-canal post-treatment was observed in patients with cervical cancer undergoing RT. • No differences were noted in width at introitus or vaginal length. • CT imaging was effective in detecting radiation-induced VS, with menopausal status and smoking history influencing the extent of dimensional changes.¹²
Miccò et al.	Retrospective cohort	43	<ul style="list-style-type: none"> • DW-MRI showed a higher diagnostic ability than TV in predicting CRT-induced VS in patients with locally advanced cervical cancer. • DW-MRI patterns differed significantly between CTCAE grades, with signal loss of the vaginal mucosa or diffuse restricted diffusion observed in grades ≥ 2. • The study suggests DW-MRI as a useful tool for early prevention and management strategies of VS in LACC patients after CRT.¹³

DISCUSSION

The studies included in this review assessed the rates of mild, moderate, and severe vaginal stenosis; factors predicting the development of vaginal stenosis; and management approaches. The combined results of these studies showed a high incidence of late vaginal stenosis, with significant rates observed at various posttreatment follow-up periods. This highlights the importance of early detection and targeted intervention to prevent vaginal stenosis. A review by Morris et al. supports our study findings on the effectiveness of interventions.^[14]

The strength of this review lies in its comprehensive analysis of a diverse range of studies involving different treatment modalities, patient populations, and follow-up durations. By synthesising these findings, we gained a broader perspective on the incidence, predictors, and management strategies for vaginal stenosis following cervical cancer treatment. However, it is important to acknowledge the

inherent limitations of this study, including heterogeneity across studies, variations in sample sizes, and inconsistent reporting of outcomes. Furthermore, the lack of uniformity in defining predictors and management approaches also contributes to the limitations of this review.

Despite these limitations, this review provides valuable insights into potential predictors and management strategies for radiation-induced vaginal stenosis. These findings support the idea that early identification of predisposing factors, such as pallor reaction grade, advanced age, and adherence to dose constraints, could help in timely management and mitigation of vaginal stenosis development. However, as per Haddad et al., controversies exist regarding the effectiveness of certain management strategies, such as vaginal dilator use, highlighting the need for further research and standardization in this area.^[15]

Future research should focus on standardising methodologies, exploring the underlying mechanisms, and conducting systematic reviews to

enhance the reliability and consistency of predictors and management strategies for radiation-induced vaginal stenosis. Further clinical research is needed to validate the specific predictors and establish their roles in routine assessments.

CONCLUSION

The high incidence of late VS underscores the importance of early identification and targeted interventions to mitigate its development. Predisposing factors, such as pallor reaction grade, advanced age, and adherence to dose constraints have been identified as significant predictors, highlighting the importance of proactive management approaches. While this synthesis offers a comprehensive overview of the current understanding of VS, it provides valuable guidance for clinicians and researchers in identifying risk factors and implementing effective management strategies.

Moving forward, standardisation of methodologies, further exploration of underlying mechanisms, and systematic reviews will be crucial for enhancing the reliability and consistency of predictors and management strategies for radiation-induced VS. Additionally, future research should focus on validating specific predictors and establishing their role in routine clinical assessments. This synthesis serves as a valuable resource for advancing our understanding of radiation-induced VS and underscores the importance of collaborative efforts and systematic approaches for improving patient care in this domain.

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