Evaluation and Treatment Protocol for Radiation Cystitis Following Pelvic Radiotherapy

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Hypothesis / aims of study

Radiotherapy aims to deliver high doses of radiation to target organs, eradicate the tumor, and respect the function of surrounding organs, preserving normal tissue tolerance (1,2). The treatment of pelvic organ cancers such as rectal cancer, prostate cancer, cervical cancer, or bladder cancer presents external pelvic radiotherapy as an important therapeutic option (2,3). The urinary bladder can be sensitive to low doses of radiation, potentially being intentionally irradiated in bladder cancer patients, or incidentally in patients with cancer involving other pelvic structures, leading to acute and/or late adverse events. Bladder lesions and symptoms following pelvic organ irradiation define radiation cystitis (RC), with severity related to the total delivered dose, volume of radiation exposure, administration scheme, and fractionation (2,4,5). This therapeutic modality predisposes to the development of neovascularization in the form of telangiectasias and bladder bleeding, along with lower urinary tract symptoms partially related to interstitial fibrosis and smooth muscle involvement , and reduced bladder capacity (figure 1 and 2). Hematuria is the main presenting symptom and can range from mild to life-threatening bleeding (5,6). Radiation-associated complications account for up to 5-10% of emergency urology admissions. The urinary bladder response to radiation treatment can be classified into acute or subacute reactions occurring within three to six months of radiation treatment, and late reactions occurring after six months to years (1,3,5). The diagnosis of radiation cystitis is based on excluding other causes of hematuria and patient symptoms, as clinical characteristics are nonspecific and may also be caused by bladder infection or cancer at other urinary tract locations. The most important examination at this stage is lower urinary tract evaluation via cystoscopy (1,5). There are several treatment options for radiation cystitis. However, the scarcity of high-quality evidence in the form of randomized clinical trials complicates the development of treatment algorithms. Treatment strategies can be divided into systemic treatments, intravesical treatments, ablative procedures, hyperbaric interventions, and interventional procedures such as definitive surgeries. The treatment goal and chosen modality depend on patient symptoms and disease stage (1,3,5,6).

The aim of this study was to prospectively evaluate the management of patients undergoing pelvic radiotherapy to develop a protocol for diagnosis, treatment, and follow-up of patients with radiation cystitis, tailored to each disease phase, and implement this tool to improve the quality of care and consequently the quality of life.

Figure 2 cystoscopic findings: erythema, edema, bleeding ulcers and fibrosis (with reduced bladder capacity)

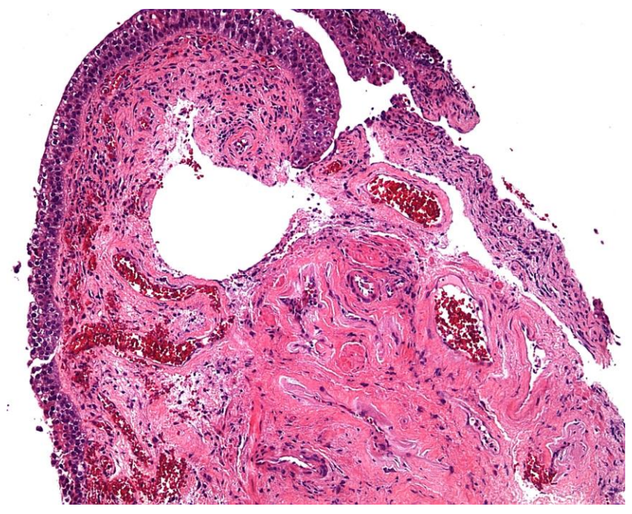

Image courtesy of Professor Athanase Bilis MD

Figure 2 Perivascular as well as diffuse fibrosis of the vesical mucosa.

Study design, materials and methods

A prospective study was conducted to establish the profile of patients with radiation cystitis at a university hospital. Volunteer patients diagnosed with pelvic organ neoplasms with an indication for radiotherapy were included. Symptoms of lower urinary tract were assessed using two validated questionnaires (ICIQ-Male LUTS and ICIQ-OAB), along with a urinary diary, at three time points: before starting radiotherapy, one week after completing radiotherapy, and six months after treatment completion. Additionally, a literature review on the treatment of radiation cystitis was conducted to identify evidence-based data supporting diagnosis and treatment. The literature search encompassed MEDLINE, Embase, PubMed, and Google Scholar to identify peer-reviewed articles investigating the epidemiology, physiopathology, diagnosis, and management of radiation cystitis. An author reviewed the title and abstract of all retrieved studies and obtained full texts of all articles. The respective bibliographies were evaluated to identify additional studies for possible inclusion. Guidelines from the American Urological Association and the European Association of Urology were also included. Case reports were excluded.

Results and interpretation

Between March 2023 and January 2024, a total of 16 patients, 3 females and 13 males, with a mean age of 66.9 ± 16 years (range 52 to 83 years), were included in the study. Ten patients received radiotherapy for prostate cancer, four for rectal cancer, and two for squamous cell carcinoma of the anal canal. Among patients treated for prostate cancer, two received a total dose of 66 Gy, one received 70 Gy, and six received 76 Gy. Patients treated for anal canal carcinoma received a total radiation dose of 54 Gy, and patients diagnosed with rectal cancer received 50.4 Gy.

Male patients responded to both questionnaires and completed a three-day urinary diary, while female patients only answered the ICIQ-OAB questionnaire and the three-day urinary diary. All assessments were performed on three different occasions, before and after pelvic radiotherapy, aiming to evaluate any worsening of lower urinary tract symptoms (LUTS) and identify patients with acute radiation cystitis (up to six months). However, there was no worsening of symptoms during treatment in any of the evaluated patients.

To establish the protocol for diagnosis and treatment management of radiation cystitis, a total of thirty-nine articles were included for review. The protocol was divided into different sections containing clinical presentation (acute phase vs. chronic phase), diagnosis, staging, systemic therapy, intravesical therapy, ablative therapy, radiologic intervention, and definitive surgical treatment, summarized in the attached algorithm (Figure 3). Currently, high-quality evidence describing the management of radiation cystitis is scarce. The definition of acute radiation cystitis includes any clinical manifestation that occurs during or up to three months after the completion of radiotherapy. Clinical symptoms comprise storage and voiding symptoms, such as increased urinary frequency, nocturia, urinary urgency, dysuria, bladder pain with spasms, and (rarely) hematuria.

According to the literature, side effects are experienced by nearly half of patients after pelvic irradiation at full curative doses. This data differs from the findings in the present study, which can be explained by advances in radiation techniques, such as high-energy linear accelerators and intensity-modulated radiotherapy, enabling the administration of increasingly effective doses to the tumor, leading to an improvement in treatment tolerance.

Although in the short term, the application of questionnaires and urinary diaries did not show a negative impact, they are validated tools that are easy to apply. Therefore, patients should be informed that if they experience changes in lower urinary tract symptoms, they should be reassessed.

Late radiation cystitis, although relatively rare, can lead to severe bleeding and may be difficult to treat. In the absence of robust evidence for any treatment modality, most patients are initially treated supportively, and many patients require multimodal treatment. Numerous treatment options have been studied over the past decades, but many patients still require surgery to stop life-threatening hematuria. Such surgeries are often associated with significant morbidity, and any alternative treatment options should be further explored. In the future, large randomized trials exploring emerging management strategies will be needed to strengthen evidence-based treatment strategies.

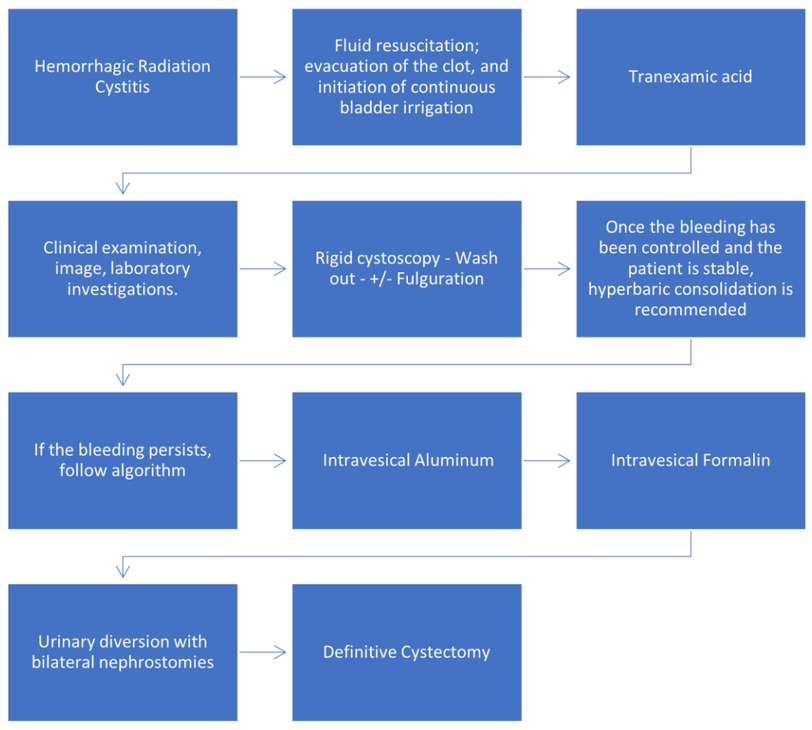

Figure 3 Algorithm for radiation-induced haemorrhagic cystitis illustrating the recommended practical management.

Conclusions

Additionally, the present study aims to help fill the existing gap in the scientific literature by offering an evidence-based protocol for the management of radiation cystitis. This can serve as a model for other healthcare institutions, promoting more effective and standardized care for patients with this post-pelvic radiotherapy condition.

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