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PILOT STUDY

FUNCTIONAL UROLOGY

Optimizing functional outcomes in prostate cancer: a new perspective on early artificial urinary sphincter implantation before salvage radiotherapy in prostate cancer treatment

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Introduction Stress urinary incontinence is a significant adverse effect following radical prostatectomy for prostate cancer. Various factors, including surgical technique and patient characteristics, influence the incidence of incontinence. Early artificial urinary sphincter implantation prior to salvage radiotherapy may improve functional outcomes and quality of life for these patients. The objective of our study is to address the current gap in research regarding the effects of radiotherapy on tissues surrounding the artificial urethral sphincter, particularly when the artificial urethral sphincter (AUS) is implanted before, rather than after, radiotherapy.

Material and methods This pilot study analysed the impact of early AUS implantation in 2 prostate cancer patients who underwent radical prostatectomy (RP) and subsequently received salvage radiotherapy (SRT) due to biochemical recurrence. Radiation dose distribution and functional outcomes, including continence rates and complications, were evaluated.

Results Both patients experienced significant improvements in continence post-AUS implantation, using fewer pads daily. However, a slight deterioration in AUS effectiveness was observed post-radiotherapy, with an increase in pad usage. Radiation doses at the cuff site were relatively low, but mild tissue reactions were noted.

Conclusions Early AUS implantation before SRT shows promise in enhancing urinary continence and overall quality of life in prostate cancer patients. Despite mild complications, the approach appears feasible and beneficial. Further studies are needed to confirm these findings and optimise treatment sequencing.

Key Words: prostate cancer ‹› stress urinary incontinence ‹› radical prostatectomy ‹› salvage radiotherapy ‹› artificial urethral sphincter

INTRODUCTION

Stress urinary incontinence represents a potential adverse effect of radical prostatectomy (RP). The incidence of this condition is influenced by various factors, including the surgeon's experience, the surgical technique, the patient's anatomical characteristics, and the stage of the prostate tumour. Data suggest that urine leakage occurs in 2.0% to 87.0% of patients immediately after catheter removal [1, 2]. While most patients experience temporary periods of incontinence after RP, the majority typically regain total continence within 2 to 3 months [3]. Numerous well-documented studies involving thousands of patients indicate that the severity of urinary incontinence decreases over time, with a gradual return to continence observed in 68.0% to 97.0% of patients at 12 months postoperatively [4–9]. Furthermore, continence may progressively improve for up to 2 years postoperatively [10].

Effective rehabilitation, which is crucial in this process, focuses on enhancing the strength and responsiveness of the sphincter muscles, but these improvements require time. It is generally acknowledged that the definitive assessment of continence should be conducted one year after surgery. Subsequently, long-term post-prostatectomy incontinence rates, as reported by various studies, range from 2.0% to 10.0% [1, 3, 4]. Beyond the first year, it is widely accepted that these rates are unlikely to show significant improvement.

The objective of our study is to address the current gap in research regarding the effects of radiotherapy on tissues surrounding the artificial urethral sphincter (AUS), particularly when the AUS is implanted before radiotherapy. This evaluation seeks to determine potential impacts and inform optimal treatment sequencing.

PERSISTENT POST-PROSTATECTOMY INCONTINENCE

In cases where appropriate rehabilitation fails to resolve urinary incontinence following radical prostatectomy, resulting in a significant detriment to the patient's quality of life, urologists may consider 2 surgical interventions.

The first option involves the insertion of a tape under the bulbar urethra, suitable for less severe cases. The second option, recommended for patients experiencing moderate to severe stress urinary incontinence, is the implantation of an AUS. The AMS 800™, manufactured by Boston Scientific, is the most widely used system. It comprises a three-part silicone device consisting of a cuff that encircles the urethra, a reservoir located in the abdominal cavity, and a pump positioned in the scrotum. Its effectiveness, according to various studies, ranges from 70.0% to 85.0% [1, 5–7].

Successful implantation of an AUS significantly enhances the patient's quality of life. However, complications occur in 21.0% to 41.1% of cases, typically arising from mechanical failures and erosion of the sphincter components into the urethra or the skin. Moreover, multivariate analyses have identified radiation for prostate cancer recurrence as an independent risk factor for urethral atrophy [1, 8, 9].

It is crucial to underscore that while efforts to restore continence are underway, patients continue to be monitored and treated for prostate cancer. The management strategy depends on the completeness of the radical prostatectomy and the postoperative prostate-specific antigen (PSA) levels. This dual approach ensures that both the functional impact of the surgery and the oncological outcomes are optimally managed, highlighting the necessity of an integrated care pathway for these patients. Current studies state that about 15.0–25.0% [11, 12] of patients after prostatectomy may need supplemental radiotherapy for the prostate bed.

TIMING OF RADIOTHERAPY

Proper patient selection for post-prostatectomy radiotherapy can significantly influence local disease control and potentially extend survival. The timing of radiotherapy on the prostate bed initiation remains an important subject of numerous studies. There are primarily 2 clinical scenarios that should be considered: adjuvant radiotherapy (ART) and salvage radiotherapy (SRT).

Adjuvant treatment, by its very nature, supplements primary or initial therapy. Its purpose is to reduce the risk of relapse, even when surgery seems to have achieved complete control. Adjuvant radiotherapy is generally administered within 4 to 6 months after radical prostatectomy, once urinary control reaches acceptable levels. This approach targets the eradication of residual cancer cells before any detectable recurrence, as shown by rising PSA levels. Conversely, SRT is reserved for cases of biochemical failure, indicated by abnormal PSA levels that suggest cancer recurrence.

Salvage radiotherapy is initiated once cancer recurrence is confirmed, with the ideal PSA threshold for starting treatment considered to be between 0.2 ng/ml and 0.5 ng/ml. This delayed approach to SRT is designed to spare many patients from unnecessary radiotherapy. Current trends, as outlined in the latest European Association of Urology (EAU) guidelines, recommend SRT as the preferred approach, with ART being applied less frequently and primarily reserved for patients with unfavourable prognostic factors identified in histopathology, such as International Society of Urological Pathology (ISUP) grade 4–5, positive surgical margins, extraprostatic extension, seminal vesicle invasion, and lymph node involvement [13].

However, it also means that irradiation may be postponed, often occurring several years post operation. Consequently, the timing of radiotherapy may coincide with the period when the implantation of an artificial sphincter due to persistent incontinence is being considered. This overlap can complicate the sequence of treatments, posing challenges in deciding the order of procedures. The timing of radiotherapy is crucial not only for optimising oncological outcomes but also for managing urinary incontinence and enhancing the overall quality of life in patients with prostate cancer. The integration of these treat-

ments must be carefully planned to address both the oncological and functional needs of the patient, thereby ensuring comprehensive care.

CASE PRESENTATIONS

The impact of radiation dose distribution was analysed in 2 patients who had been submitted to AMS 800™ implantation and later were qualified for SRT of the prostate fossa due to biochemical recurrence.

Patient 1

The first patient, a 70-year-old male, had a radical prostatectomy in June 2015. The postoperative pathology report described Gleason 4 + 3, pT3aN0Mx, and R0. After the operation, the patient suffered from urinary incontinence grade II (leaking while standing). After 14 months of intensive rehabilitation, the situation did not improve significantly, with the need to use 9 pads daily.

AMS 800™ implantation was performed in February 2017. Postoperatively, the number of pads decreased to 0–1 daily, and the quality of life significantly improved. At the same time, the patient was under PSA follow-up, which started to rise in 2017, and on April 2018 it reached 0.35 ng/ml, suggesting biochemical recurrence. The MRI done in January 2018 did not add much information about a possible macroscopic recurrence. In July 2018 the patient was submitted to radiotherapy to the prostate bed. A follow-up of 9 months did not reveal any significant complications. The patient's PSA level decreased to 0.14 ng/ml until February 2019. The AUS effectiveness had slightly deteriorated several weeks after the irradiation; the patient began using 2 to 3 pads a day and experienced mild discomfort around the sphincter area. However, he remained satisfied with his overall urinary control. No further complications related to the implantation of the artificial urethral sphincter were observed.

Unfortunately, in March 2019, the patient was admitted to the intensive care unit from the gastroenterology clinic due to a rapidly worsening general condition and increasing respiratory failure following acute pancreatitis. Despite conservative treatment in the gastroenterology clinic, the patient's condition deteriorated, leading to anuria unresponsive to furosemide, intubation for respiratory support, and initiation of continuous renal replacement therapy (CRRT); however, the patient's condition continued to decline, culminating in death due to cardiovascular collapse and asystole in March 2019. This event was not associated with prostate cancer history or therapy.

Patient 2

In the second case, a male aged 63 years had a radical prostatectomy performed in February 2016. The postoperative pathology report stated adenocarcinoma Gleason 4 + 3, T2N0M0, and R0. The PSA 6 weeks after the operation was <0.003 ng/ml. Urinary incontinence of grade II was present after the operation, and the patient needed 6–8 pads a day. Rehabilitation lasted for 12 months, but the patient was still using 6 pads a day.

Due to persistent urinary incontinence and no signs of prostate cancer recurrence, the patient had an AMS 800™ implanted on 10 October 2017. In the postoperative period, the patient reported needing to use approximately 3 pads a day, but he was satisfied with the surgical outcome. A standard post-prostatectomy oncological follow-up was continued. In February of 2020, an MRI performed due to the rise of PSA to 0.72 ng/ml did not reveal any sign of local recurrence. However, in May 2020, his PSA increased to 1.75 ng/ml. Subsequent bone scans and PET-PSMA did not show signs of macroscopic tumour relapse. The patient was referred to radiotherapy. He finished the course in September 2020. Similarly, to our first patient, this patient did not achieve full continence and needed to use approximately 3 pads a day, but he was satisfied with the implanted AUS.

Evaluation of radiation therapy dose distribution

In both cases, irradiation with a linear accelerator of 6 MV energy was employed, utilising modern conformal techniques like intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT). The planning was based on CT scans obtained in the therapeutic position of the patient with a full bladder, using the Eclipse planning system. Because in both patients the local recurrence site was not found in any diagnostic exams, radiotherapy was prescribed to the prostate bed with a boost to vesicourethral anastomosis, where the relapse usually occurs [14].

A typical simultaneous integrated boost for prostate cancer (SIBRT) technique was used with 63 Gy/28 fr for the prostate bed and 66 Gy/28 fr for the anastomosis. Figures 1B, and 2B present the localisation of AUS elements in relation to high-dose regions. Figure 1 represents the radiation therapy dose distribution in the first patient, and Figure 2 depicts the dose distribution in the second patient.

In each instance, the components of the AUS were carefully mapped to assess the radiation doses received. In both cases, the AUS cuff was positioned

in its standard location within the bulbar urethra, approximately 30 mm from the vesicourethral anastomosis. The cuff, being the most critical and vulnerable part of the AUS, frequently undergoes cycles of inflation and deflation, exerting recurrent pressure on the urethra and thereby inducing mechanical and ischaemic stress. Consequently, monitoring the radiation dose to the tissue surrounding this component is crucial due to its susceptibility to erosion. In both cases, the radiation dose at the cuff was

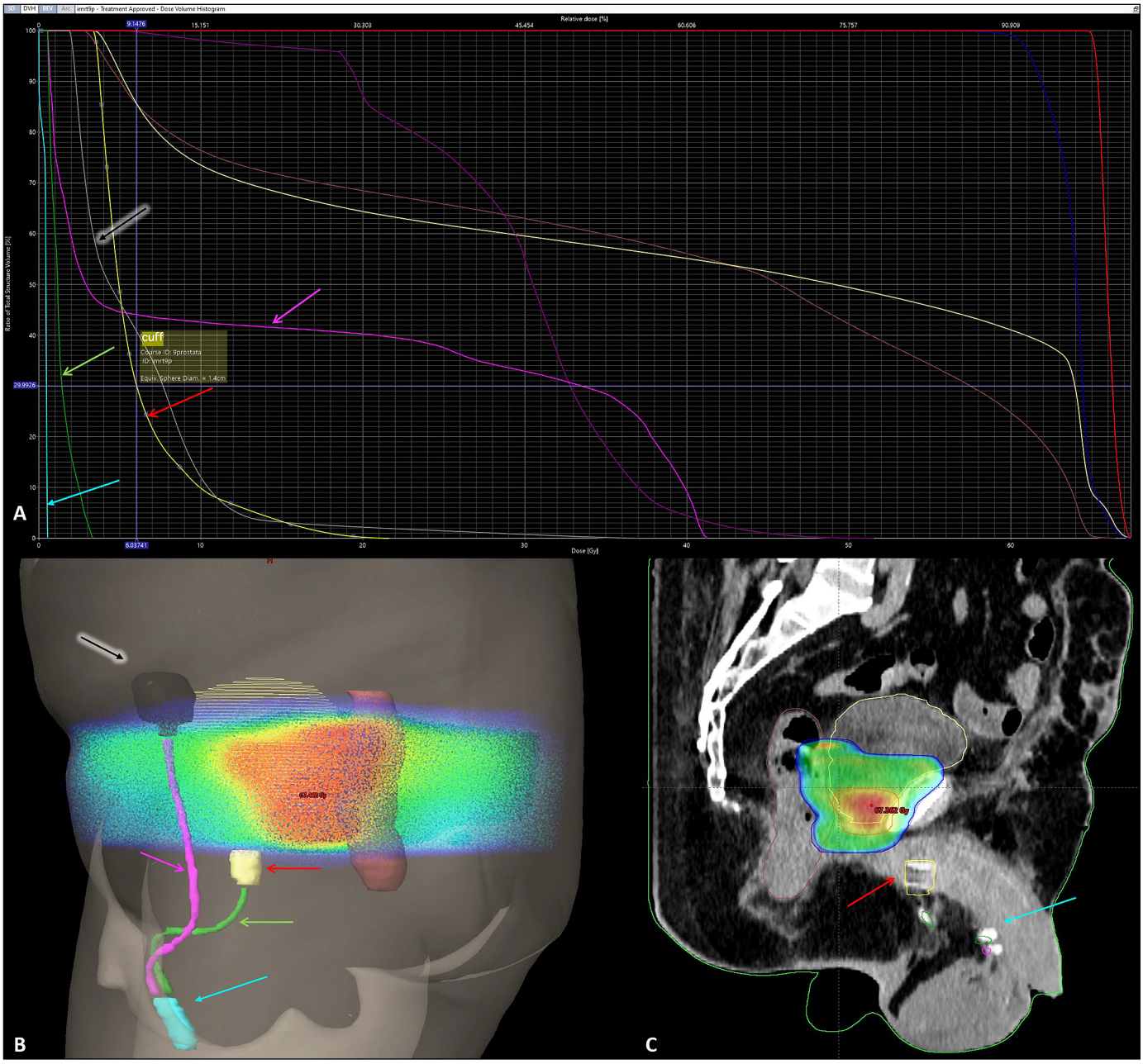

Figure 1. *Radiation dose distribution for patient 1.* **A)** *Dose-volume histogram for patient 1 showing radiation dose distribution to the AMS 800™ artificial urethral sphincter (AUS) components during salvage radiotherapy. The red arrow indicates the dose to the AUS cuff. The light blue arrow denotes the control pump, green and pink arrows indicate the cuff tubing and balloon tubing, the red arrow represents the cuff, and the black arrow identifies the pressure-regulating balloon.* **B)** *3D dose distribution model illustrating the spatial relationship between AUS components and irradiated regions. The red arrow points to the AUS cuff, the green and pink arrows indicate cuff tubing and balloon tubing, respectively, the light blue arrow indicates the control pump, and the black arrow shows the pressure-regulating balloon.* **C)** *Computed tomography scan with dose overlay, highlighting the AUS cuff (red arrow) near high-dose regions.*

relatively low, with minimum and maximum doses of 3.3 Gy and 21.6 Gy, respectively, with mean dose 6 Gy in the first case (Figure 1A, red arrow), and minimum and maximum doses of 2.4 Gy and 4.7 Gy, respectively, with a mean dose of 3.8 Gy in the other (Figure 2A, red arrow).

As expected, the radiation doses to other parts of the AUS were even lower. The relationship between dose and volume for each part of the AUS is presented on a dose-volume histogram (DVH) – coloured curves in Figures 1A and 2A, and as 3D dose distribution models in Figure 1B and 2B.

In Figure 1, illustrating the radiation distribution in the first patient, a light blue arrow denotes the control pump, green and pink arrows indicate the cuff tubing and balloon tubing, a red arrow represents the cuff, and a black arrow identifies the pressure-regulating balloon. In Figure 2, the yellow arrow signifies the control pump, green and pink arrows denote the cuff tubing and balloon tubing, a red arrow indicates the cuff, and a black arrow marks the pressure-regulating balloon. Additionally, Figure 1C displays a CT scan with the dose overlay and the AUS cuff highlighted by a red arrow.

Dose-volume histogram interpretation

Due to its susceptibility to damage, the AUS cuff (Figures 1A and 2A, red arrow) should especially be protected from excessive radiation exposure. On the DVH, the x-axis represents the dose received, measured in Gy, while the y-axis denotes the percentage of the volume of the AUS cuff receiving a specific dose. In the radiotherapy planning process, it is crucial to keep the dose to the AUS as low as possible; nevertheless, due to the close location of the cuff to the prostate bed, some exposure to radiotherapy is unavoidable (Figure 1A, red arrow). Despite meticulous planning of the radiotherapy field, a small part of the cuff received a maximum of 21.6 Gy, indicating only partial sparing. Importantly, as described earlier, it appears that such a dose did not affect the functionality of the cuff in the follow-up and did not lead to urethra erosion.

In the second case, as presented in Figure 2, only the pressure-regulating balloon (black arrow) received a notable dose of radiation, while other parts of the AUS system were effectively protected.

A graphical representation of the 3D dose distribution model is shown in Figures 1B and 2B; the spatial distribution of the radiation dose is shown in a colour gradient. The region of the AUS cuff is again marked by a red arrow. The model highlights the intended distribution of radiation and

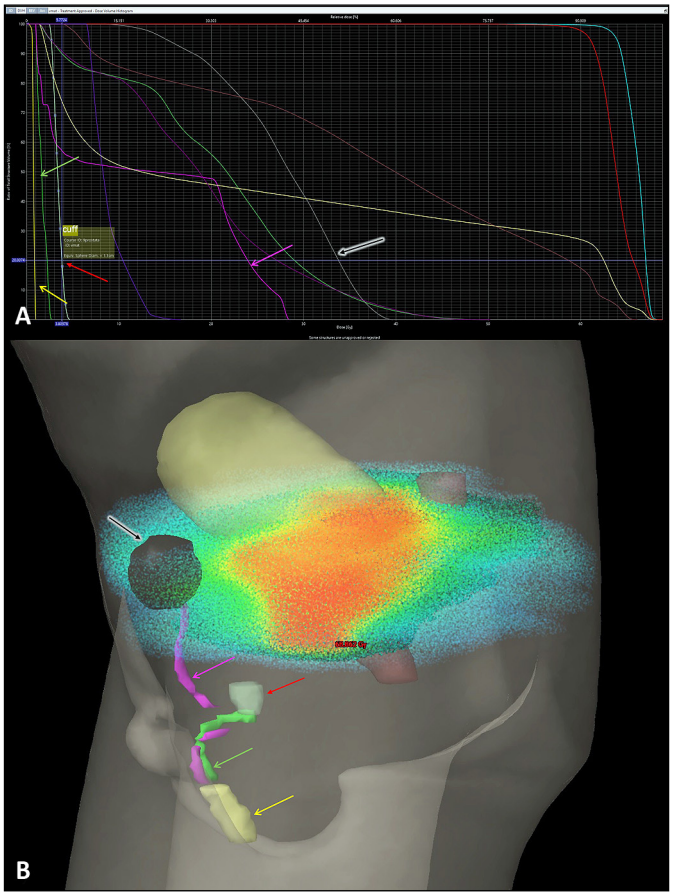

Figure 2. *Radiation dose distribution for patient 2.* **A)** *Dose-volume histogram for patient 2 showing radiation dose distribution to the AMS 800™ artificial urethral sphincter (AUS) components during salvage radiotherapy. The red arrow indicates the dose to the AUS cuff. The yellow arrow signifies the control pump, the green and pink arrows denote the cuff tubing and balloon tubing, and the black arrow marks the pressure-regulating balloon.* **B)** *3D dose distribution model depicting the AUS components' exposure to radiation. The red arrow indicates the dose to the AUS cuff. The yellow arrow signifies the control pump, the green and pink arrows denote the cuff tubing and balloon tubing, and the black arrow marks the pressure-regulating balloon. The colour gradient from blue (lower dose) to red (higher dose) illustrates the radiation distribution.*

the overlapping sensitive structures. The colour gradient from blue (lower dose) to red (higher dose) indicates that the cuff in the first case, which is supposed to be safeguarded, is in proximity to areas receiving moderate to high doses, confirming the observations from the DVH.

These observations may also be seen in the CT scan with the dose overlay that presents a cross-sectional view, where the internal structures are visualised along with the dose distribution. The AUS cuff, highlighted by the yellow arrow, is adjacent to re-

gions receiving significant radiation. The overlay confirms that while efforts were made to minimise exposure, the cuff still receives a considerable dose, as indicated by the colour contours extending into its vicinity.

DISCUSSION

Two pivotal and unresolved issues warrant focused discussion: the relatively low radiation doses leading to significant tissue reactions in the region of AUS cuff, and the decision-making process regarding the sequence of radiotherapy and surgical intervention. Urinary incontinence complicates the safe administration of radiotherapy following radical prostatectomy because it impairs bladder filling. Conversely, the tissue reactions caused by radiotherapy can hinder the recovery of the urethral sphincter, necessitating a delay in radiotherapy until continence is restored. When urinary leakage is severe, patients may experience a prolonged deterioration in quality of life. This issue becomes even more complex if, months or years after the prostatectomy, there is a gradual increase in PSA levels, raising questions about the timing of irradiation. Such circumstances might further delay decisions regarding the implantation of an AUS. Currently, most AUS implantations occur after radiotherapy; however, this sequence is not mandatory.

Our research raises the question of whether implantation before or after radiotherapy might better meet the needs of patients and treating physicians. Although there are extensive data supporting AUS implantation post radiotherapy, it is well documented that irradiation in this region significantly increases complication rates due to early and late tissue reactions. These reactions predominantly affect the tissues around the cuff placed around the urethra, located closest to the irradiated area. As presented in this study, despite efforts made to minimise exposure, the cuff still receives a significant dose of radiation.

Future strategies should focus on optimising the dose distribution to ensure that critical components such as the AUS cuff are adequately spared to prevent potential complications and maintain their functionality. The impact of even minimal radiation doses at the sphincter site remains unclear. It is uncertain whether the complications arise more from radiation-induced tissue changes or from surgical interventions in irradiated zones. This ambiguity underscores the need for further studies to optimise the sequencing of treatments to enhance patient outcomes and minimise complications.

Tissue reactions and radiation dose implications

Despite the administration of relatively low doses of radiation delivered to the site of future AUS cuff, there is a documented increase in cuff erosion post implantation. This observation raises questions about the underlying mechanisms of tissue vulnerability post radiation.

Radiation therapy, even at low doses, induces a spectrum of biological responses that can compromise tissue integrity and healing capacity. These responses include enhanced inflammatory reactions, increased fibrosis, and vascular changes leading to decreased blood supply, and can collectively predispose the tissue to erosion when subjected to the mechanical stresses imposed by an AUS cuff. Furthermore, the irradiated tissue may exhibit altered biomechanical properties, such as reduced elasticity and compliance, which are critical factors in the context of an implanted device that cyclically compresses the urethra. The juxtaposition of mechanically stressed, less compliant tissue with an AUS device could be a plausible explanation for the increased incidence of erosions observed in clinical settings. It is imperative to explore the threshold levels of radiation that can precipitate such deleterious effects and to identify potential protective strategies that could be implemented during radiotherapy planning.

Surgical timing: irradiated versus pre-irradiated tissue

The dilemma regarding whether to operate on irradiated tissue or to irradiate previously operated tissue is complex and multifaceted. Operating on irradiated tissue involves challenges such as diminished tissue quality and impaired wound healing, which are known consequences of radiation. These factors can increase the technical difficulty of the surgery and the risk of postoperative complications.

Conversely, irradiating tissue that has already undergone surgical intervention with AUS implantation raises concerns about the radiation's impact on the integrity and functionality of the implanted device, as well as the potential for exacerbated tissue damage leading to increased complication rates. The surprisingly small number of studies addressing this dilemma has inspired us to start looking into it. The decision-making process in this context must carefully consider the individual patient's oncological prognosis, the severity of urinary incontinence, and the potential risks associated with each approach. Personalised treatment plans that incorporate detailed assessments of tissue viability, the

timing of PSA recurrence, and the specific characteristics of the AUS device are essential. Multidisciplinary teams comprising urologists, radiation and medical oncologists, and radiologists must collaborate to optimise treatment sequences that maximise oncological control while minimising functional morbidity.

CONCLUSIONS

While traditional protocols often recommend the implantation of AUS after radiotherapy, not before, we propose a re-evaluation of this sequence. Given the recent recommendations to favour salvage radiotherapy over adjuvant radiotherapy, radiotherapy is now often delayed by months or even years. This delay increases the likelihood that patients may need AUS implantation due to persistent incontinence before receiving radiotherapy. Implanting an AUS prior to radiotherapy may offer benefits aligned with improved quality of life.

Considering the complexities associated with radiotherapy's impact on the AUS, particularly the urethral cuff, and the limited data on the effects of radiation on pre-implanted AUS, there is a clear necessity for further empirical research. Future studies should include retrospective analyses of patients who have undergone these treatments in varying sequences to gather preliminary data and insights. Most importantly, prospective research is essential to providing a robust evidence base that can guide clinical decisions. Such studies would ideally compare the outcomes of AUS implantation both before and after radiotherapy, offering a clearer understanding of the potential risks and benefits.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICAL APPROVAL STATEMENT

Ethical approval was not required.

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