해부 · 생물인류학 제 38 권 제 2 호
Anat Biol Anthropol Vol. 38, No. 2 (2025) pp. 61~67
https://doi.org/10.11637/aba.2025.38.2.61

Check for updates

Review Article

Anatomical Importance of the Bladder and Strategies to Minimize Toxicity in Pelvic Radiotherapy for Prostate Cancer: A Narrative Review

Sang Jun Byun[1]

[1]*Department of Radiation Oncology, Keimyung University School of Medicine*

Abstract : Pelvic radiotherapy is a widely used curative treatment for prostate cancer. Due to its close anatomical proximity to the prostate, the bladder is highly susceptible to radiation-induced toxicity. Its variable volume and shape significantly influence dose distribution and the position of adjacent organs including the small bowel, making it a critical organ at risk during treatment planning. This review highlights the anatomical features and physiological functions of the bladder relevant to radiotherapy, the mechanisms of radiation-induced bladder injuries, and current strategies to minimize toxicity. Strategies to reduce bladder toxicity include consistent bladder filling or emptying protocols, with clinical studies supporting the feasibility of both. Empty bladder protocols have shown non-inferior outcomes in selected patients, improving setup reproducibility and patient compliance. Meanwhile, bladder filling helps reduce the dose to the bladder wall and displace small bowel from high-dose area. Bladder volume monitoring using cone-beam computed tomography (CBCT) or ultrasonography (US) allows for daily assessment of volume consistency. In particular, US offers a non-invasive, rapid alternative that correlates well with CBCT measurements. In summary, the bladder's anatomical and functional variability presents both challenges and opportunities in prostate cancer radiotherapy. Integration of individualized preparation protocols and real-time imaging strategies is essential to reduce toxicity, enhance treatment accuracy, and improve patient outcomes.

Keywords : Bladder, Anatomy, Prostate cancer, Radiotherapy, Toxicity

INTRODUCTION

Radiotherapy is one of the three main treatment modalities for cancer, along with surgery and chemotherapy. It offers the advantages of being non-invasive compared to surgery and provides a more localized treatment than systemic chemotherapy. However, the characteristics of radiation inherently expose adjacent normal tissues to unintended doses [1]. With advances in image-guided and intensity-modulated radiotherapy (IMRT), it has become possible to escalate tumor dose while minimizing normal tissue damage, although such precision requires daily reproducibility of the target and organ positioning [1,2].

Pelvic external beam radiotherapy (EBRT) plays a standard and often definitive role in the treatment of localized and locally advanced prostate cancer, often combined with

The author(s) agree to abide by the good publication practice guideline for medical journals.
The author(s) declare that there are no conflicts of interest.
Received: May 21, 2025; **Revised:** June 14, 2025; **Accepted:** June 18, 2025
Correspondence to: Sang Jun Byun (Department of Radiation Oncology, Keimyung University School of Medicine, Daegu 42601, Republic of Korea)
E-mail: ro.kryph@gmail.com

ISSN 2671-566X (Online)

androgen deprivation therapy [3]. It is frequently used either as a primary modality or in the adjuvant or salvage setting after surgery. Conventionally fractionated radiotherapy delivers 70~80 Gy over 7~8 weeks, but the low alpha/beta ratio of prostate cancer has led to increasing use of hypofractionated and even stereotactic body radiotherapy (SBRT) regimens, which require strict anatomical reproducibility [4].

Given the anatomical proximity of the prostate to the bladder and rectum, managing radiation exposure to these organs is a critical component of treatment planning. The bladder lies anatomically adjacent to the prostate and is particularly susceptible to radiation-induced injury [5]. Its thin urothelial lining and richly vascularized muscular wall make it prone to both acute and chronic injuries. Its volume fluctuates significantly based on urine content, influencing both dose distribution and neighboring organ positions including small bowels [6]. Radiation-induced bladder toxicities such as cystitis, hematuria, urinary urgency, and frequency significantly impact patient quality of life and may even lead to treatment interruptions [7].

This is a narrative review, not a systematic/meta-analysis and aims to summarize the anatomical and physiological characteristics of the bladder in the context of pelvic radiotherapy for prostate cancer and to explore strategies for minimizing bladder toxicity.

ANATOMY AND PHYSIOLOGY OF THE BLADDER

The bladder is a hollow organ with a thick muscular wall that functions to collect urine produced by the kidneys via the right and left ureters and expel it from the body through the urethra [8]. When empty, the bladder is located within the lesser pelvis. Its anterior surface lies adjacent to the pubic symphysis, and its superior aspect is covered by peritoneum [9]. In males, the vas deferens and seminal vesicles are situated between the base of the bladder and the rectum, while the bladder neck—the lowest part of the bladder—connects to the urethra and sits directly above the prostate [9]. As urine accumulates, the bladder expands upward into the greater pelvis through the extraperitoneal fat of the anterior abdominal wall, and when fully distended, it may reach the level of the umbilicus [10]. Functionally, it serves both a reservoir role and participates in coordinated micturition under autonomic control. The bladder is also composed of several layers, including the innermost urothelium, a submucosal connective tissue layer, a muscular detrusor layer, and an outer serosal surface [6]. The urothelium acts as a barrier to urine components, while the detrusor muscle facilitates coordinated contractions during voiding.

RADIATION-INDUCED BLADDER TOXICITIES

Radiation therapy for prostate cancer often involves incidental exposure of the bladder due to its close anatomical proximity. This can result in radiation-induced cystitis, which is broadly categorized into acute and late (chronic) toxicities. Acute bladder toxicities typically manifest during or within 3 months of completing treatment and include symptoms such as urinary urgency, frequency, dysuria, and low-grade hematuria [11]. These symptoms are usually self-limited and resolve after the completion of therapy [5]. In contrast, late toxicities can occur 3 months later or even years after treatment and may present with persistent hematuria, decreased bladder compliance, incontinence, fibrosis, or, in severe cases, ulceration and fistula formation [5,12,13].

The underlying pathophysiology differs between the acute and chronic phases. Acute injuries are characterized by mucosal inflammation, edema, and increased vascular permeability [14]. Chronic toxicities are attributed to progressive endothelial damage, obliterative endarteritis, submucosal fibrosis, and angiogenesis, which result in increased vessel fragility and structural bladder changes [5]. These pathological changes often underlie the persistent or recurrent hematuria observed in chronic radiation cystitis [5,15,16].

The incidence and severity of radiation-induced bladder toxicity vary depending on radiation dose, technique, and indiidual patient factors. The incidence of grade ≥ 2 or higher acute genitourinary toxicity in patients undergoing definitive radiotherapy for prostate cancer has been reported in the literature to range from 6% to 41%, reflecting considerable variability across studies. For example, a comparative study demonstrated that 30.8% of men receiving primary prostate radiotherapy experienced grade ≥ 2 acute urinary toxicity, significantly higher than the 14.0% observed in patients treated post-prostatectomy ($p<0.001$) [17]. In terms of late toxicity, a meta-analysis showed that the incidence of grade ≥ 2 late urinary toxicity varied widely, with a mean rate of around 17%, ranging from 6% to 41% depending on the specific patient population and treatment parameters [18]. These findings highlight the considerable burden of both acute and late urinary side effects in prostate cancer patients receiving pelvic radiotherapy, underscoring the importance of identifying and managing individual risk factors. Toxicities are most commonly graded using the Common Terminology Criteria for Adverse Events (CTCAE) or Radiation Therapy Oncology Group (RTOG) systems, which guide clinical management based on symptom severity [19].

STRATEGIES TO MINIMIZE BLADDER TOXICITY: EMPTY BLADDER VERSUS FILLING BLADDER

Filling the bladder prior to treatment helps displace small bowels out of the radiation field and reduces the proportion of bladder wall receiving high doses. It requires patient adherence to drinking and timing protocols. Braide et al. conducted a prospective clinical trial to evaluate the effectiveness of different bladder filling strategies in maintaining bladder volume consistency during postoperative radiotherapy in prostate cancer patients [20]. The study included 29 patients who had experienced biochemical recurrence following radical prostatectomy and were receiving EBRT to the prostate bed. Patients were assigned to one of two bladder preparation protocols: one group was instructed to void and then drink 300 mL of water one hour prior to treatment, while the other group was allowed to maintain a comfortably full bladder without specific instructions. Bladder volumes were measured using weekly CBCT imaging throughout the treatment course. The results showed no significant difference in mean bladder volume or variability between the two groups. Moreover, changes in bladder volume did not adversely affect clinical target volume coverage or treatment accuracy. These findings suggest that a flexible bladder filling approach may be sufficient in the postoperative setting, offering a patient-friendly alternative to strict hydration protocols without compromising treatment quality.

On the contrary, empty bladder protocols involve administering radiotherapy immediately after urination, making it one of the most effective methods for maintaining bladder volume reproducibility and improving patient compliance with treatment. Chetiyawardana et al. reported a retrospective study to investigate the feasibility and clinical outcomes of an empty bladder protocol in the radiotherapy of prostate cancer [21]. The study included 90 patients with low- or intermediate-risk prostate cancer who received 60 Gy in 20 fractions directed to the prostate and seminal vesicles. Patients were divided into two groups based on bladder preparation: one instructed to void immediately before treatment (empty bladder group, $n=49$), and the other to follow a bladder filling protocol (full bladder group, $n=41$). After a median follow-up of 48 months, there were no statistically significant differences between the two groups in terms of biochemical progression-free survival or the rates of grade ≥ 2 genitourinary and gastrointestinal toxicities. The findings suggest that an empty bladder protocol may serve as a clinically acceptable alternative to the conventional filled bladder approach, particularly in selected patients receiving prostate-only radiotherapy. In addition to demonstrating non-inferiority in both efficacy and safety, the study highlights the potential advantages of reduced setup time and improved patient compliance with empty bladder preparation. However, it is worth noting that the study population excluded high-risk patients and those undergoing pelvic nodal irradiation, thus limiting the generalizability of these results to broader clinical settings.

Recently, there were a few more studies on prostate cancer radiotherapy highlighting the importance of bladder management. The REFILL PAC HYPO trial is a prospective, multi-center phase II study assessing a smartphone-based reminder app designed to improve bladder filling in prostate cancer patients receiving hypofractionated radiotherapy [22]. The app sends alerts 45 minutes before treatment to prompt patients to drink 300 mL of water. With 27 patients targeted for enrollment, the study aims to reduce the frequency of sessions with inadequate bladder filling (<200 mL) by 30%, and will evaluate patient adherence, satisfaction, and perceptions of digital health, using a historical control for comparison. A separate retrospective study of 275 patients analyzed the effects of bladder volume and shape on setup consistency during radiotherapy. Using CBCT imaging, bladders were classified as elongated, spherical, or oval. Both volume and shape were associated with setup errors, but bladder shape had a stronger impact (OR 2.013 vs. 1.470). Spherical bladders showed the most positional variability and the lowest shape consistency. The study underscores the need for bladder preparation strategies that account for both volume and morphology to minimize setup errors and treatment interruptions [23].

Based on previously published studies, clinicians should

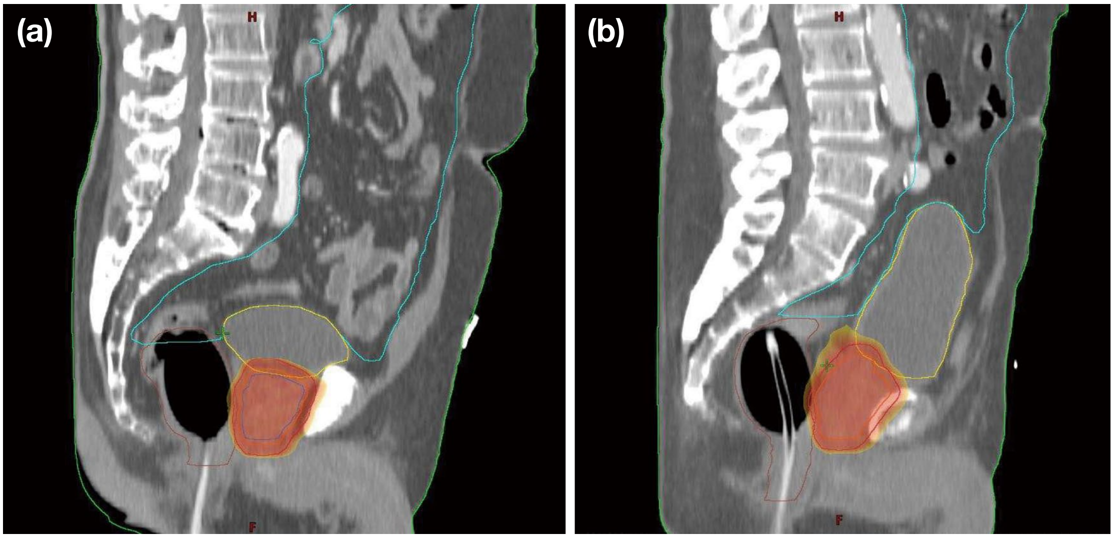

Fig. 1. The figures present representative sagittal images comparing the empty bladder (a) and filling bladder (b) protocols, respectively. In these images, the bladder is delineated in yellow, the rectum in brown, and the bowel in cyan. The red-shaded region indicates the high-dose radiation area. As illustrated, the filling bladder protocol effectively reduces the proportion of the bladder volume exposed to high-dose irradiation while simultaneously displacing the bowel in a superior direction. This anatomical shift contributes to enhanced sparing of adjacent normal tissues and may lead to a reduction in radiation-induced toxicity.

Table 1. Comparison of empty and full bladder preparation protocols in pelvic radiotherapy

	Empty bladder protocol	Filling bladder protocol
Reproducibility	Generally more reproducible due to consistent bladder status	Potentially variable; depends on patient hydration and compliance
Patient comfort	More comfortable—no need to retain urine	Less comfortable, patients must drink water and hold urine before treatment
Setup time	Faster preparation; minimal pre-treatment delay	Longer preparation time due to hydration and waiting for bladder filling
Bladder wall dose	Higher proportion of bladder wall receives high-dose radiation	Larger bladder reduces high-dose exposure to bladder wall
Small bowel sparing	Small bowel may reside closer to radiation field	A full bladder can push bowel out of high-dose region, reducing toxicity risk
Individual variation	Less affected by patient-specific bladder volume	Requires individualized planning due to varying bladder capacities

appropriately select between the two protocols to optimize the delivery of radiotherapy. The characteristics of the two protocols are summarized in Fig. 1 and Table 1. While the empty bladder protocol may offer practical advantages in terms of patient comfort and reduced preparation time, the widespread implementation of CBCT and IMRT now facilitates individualized treatment planning. These advanced techniques enable the delivery of highly precise radiotherapy while simultaneously minimizing patient burden and treatment-related toxicity.

BLADDER VOLUME MONITORING USING CBCT AND US

Bladder volume variability is a well-documented challenge in prostate cancer radiotherapy, as changes in bladder filling can affect both target positioning and radiation exposure to surrounding organs. Volume monitoring is most commonly performed using daily imaging modalities such as CBCT. In a study by Chen et al., 314 CBCT scans from 19 prostate cancer patients were analyzed to evaluate interfractional changes in bladder and rectal volumes [24]. The results revealed significantly greater variation in bladder volume compared to rectum, which corresponded to proportional fluctuations in mean bladder dose. These findings underscore the importance of consistent bladder preparation to avoid unintentional overdose to the bladder and ensure dosimetric accuracy during treatment. Furthermore, Heng et al. examined the impact of standardized bowel and bladder preparation protocols on organ volume consistency [25]. In this study, 12 prostate cancer patients were divided into two groups, with only one group following specific bladder and bowel preparation guidelines. The non-protocol group exhibited significantly greater variability in bladder and rectal volumes, which translated into inconsistencies in radiation dose delivery. These findings emphasize that preparation protocols are essential not only for organ reproducibility but also for optimizing treatment accuracy and minimizing toxicity risks.

Additionally, US imaging has also emerged as a practical, non-invasive tool for monitoring bladder volume during radiotherapy in prostate cancer patients. In a prospective study, Chauhan et al. evaluated 29 patients receiving EBRT, comparing daily bladder volume measurements using both US and CBCT [26]. The study found a strong correlation between the two modalities ($r=0.85$), supporting the reliability of US as an alternative to CBCT for bladder assessment. However, bladder volumes during treatment were consistently lower than simulation values, and older patients showed greater difficulty maintaining adequate filling, suggesting that individualized bladder protocols may be necessary.

Similarly, Bodusz et al. conducted a large-scale evaluation involving 142 patients undergoing stereotactic radiosurgery [27]. Bladder volumes were assessed using ultrasound across 1,344 sessions. The mean bladder volume measured via US was significantly lower than the planning volumes from CT simulation, yet daily US scans helped ensure treatment reproducibility. The authors emphasized that ultrasound-based bladder volume control should be considered a standard part of prostate cancer radiotherapy, particularly in high-precision treatments like SBRT. Reilly et al. further explored the predictive value of daily ultrasound in post-prostatectomy radiotherapy [28]. Their study demonstrated that pre-treatment ultrasound imaging could anticipate whether dosimetric endpoints for bladder and rectum would be met, reducing the need for frequent CBCT scans. This approach enhances workflow efficiency while supporting consistent organ positioning. Collectively, these findings validate the clinical utility of ultrasound for real-time bladder volume monitoring, enabling more adaptive and patient-tailored treatment strategies.

FUTURE DIRECTIONS

Bladder management continues to be a key consideration in pelvic radiotherapy for prostate cancer, and ongoing technological advancements offer promising avenues for improving treatment precision, reproducibility, and patient outcomes. One of the most rapidly evolving areas is adaptive radiotherapy (ART), which allows for individualized treatment adaptation based on daily anatomical changes. This is particularly relevant in prostate cancer, where bladder and rectal filling can significantly alter the position of the target volume. ART, facilitated by daily CBCT or magnetic resonance imaging (MRI)-guided systems, has demonstrated the ability to maintain consistent dosimetric coverage while minimizing exposure to adjacent organs at risk [29]. Incorporating deformable image registration and auto-segmentation, ART could be especially beneficial for patients with large inter-fractional variability in bladder filling.

In parallel, the integration of artificial intelligence (AI) and machine learning (ML) in radiotherapy is gaining momentum. These technologies offer the potential to analyze large datasets from imaging, treatment planning, and clinical outcomes to develop predictive models of bladder motion, toxicity risk, and treatment response. For instance, ML algorithms have been used to identify patterns of bladder volume variability and predict when adaptive replanning might be necessary [30]. Additionally, AI may assist in automating contouring and optimizing dose distributions, further enhancing workflow efficiency and standardization across institutions.

CONCLUSION

The bladder plays a critical anatomical and functional role in the radiotherapeutic management of prostate cancer. Due to its close proximity to the prostate and its dynamic volume changes, it is highly susceptible to radiation-induced injury. Advances in radiotherapy techniques, including image-guided radiotherapy, IMRT, and ART, have enabled better sparing of the bladder while maintaining precise tumor targeting. Multiple strategies have been developed to reduce bladder toxicity, including consistent bladder filling or emptying protocols, real-time volume monitoring using CBCT or US, and adaptive planning techniques based on daily anatomical changes. Clinical studies support the feasibility of both empty and full bladder protocols depending on treatment context, and emerging evidence from MRI-guided and AI-supported ART further underscores the importance of individualized treatment approaches.

Continued refinement of bladder management protocols, integration of non-invasive imaging, and technological innovations will be essential for improving treatment reproducibility, reducing toxicity, and ultimately enhancing the quality of life and outcomes for prostate cancer patients receiving pelvic radiotherapy.

REFERENCES

1. Sanghani M, Mignano J. Intensity modulated radiation therapy: a review of current practice and future directions. Technol Cancer Res Treat. 2006;5:447-50.
2. Jaffray DA. Image-guided radiotherapy: from current concept to future perspectives. Nat Rev Clin Oncol. 2012;9:688-99.
3. Schmidt-Hegemann NS, Zamboglou C, Mason M, Mottet N, Hinnen K, De Meerleer G, et al. ESTRO-ACROP recommendations for evidence-based use of androgen deprivation therapy in combination with external-beam radiotherapy in prostate cancer. Radiother Oncol. 2023;183:109544.
4. Cho LC, Timmerman R, Kavanagh B. Hypofractionated external-beam radiotherapy for prostate cancer. Prostate Cancer. 2013;2013:103547.
5. Zwaans BMM, Nicolai HE, Chancellor MB, Lamb LE. Prostate cancer survivors with symptoms of radiation cystitis have elevated fibrotic and vascular proteins in urine. PLoS One. 2020;15:e0241388.
6. Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. Physiol Rev. 2004; 84:935-86.
7. Helissey C, Cavallero S, Brossard C, Dusaud M, Chargari C, François S. Chronic inflammation and radiation-induced cystitis: molecular background and therapeutic perspectives. Cells. 2020;10.
8. Ramakrishnan VM, Eswara JR. Basic bladder physiology and anatomy. In: Stoffel JT, Dray EV, editors. Urological care for patients with progressive neurological conditions. Cham: Springer International Publishing; 2020. p. 7-15.
9. Woodburne RT. Anatomy of the bladder and bladder outlet. J Urol. 1968;100:474-87.
10. Pannu HK, Oliphant M. The subperitoneal space and peritoneal cavity: basic concepts. Abdom Imaging. 2015;40:2710-22.
11. Viswanathan AN, Yorke ED, Marks LB, Eifel PJ, Shipley WU. Radiation dose-volume effects of the urinary bladder. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S116-22.
12. Gatsinga R, Lim BJH, Kumar N, Tan JGG, Li Y, Wang MLC, et al. Radiation-induced hemorrhagic cystitis in prostate cancer survivors: the hidden toll. Medicina (Kaunas). 2024;60.
13. Maitre P, Maheshwari G, Sarkar J, Singh P, Kannan S, Dutta S, et al. Late urinary toxicity and quality of life with pelvic radiation therapy for high-risk prostate cancer: dose-effect relations in the POP-RT Randomized phase 3 trial. Int J Radiat Oncol Biol Phys. 2024;120:537-43.
14. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2018;9:7204-18.
15. Alesawi AM, El-Hakim A, Zorn KC, Saad F. Radiation-induced hemorrhagic cystitis. Curr Opin Support Palliat Care. 2014;8: 235-40.
16. Voyant C, Biffi K, Leschi D, Briançon J, Lantieri C. Dosimetric uncertainties related to the elasticity of bladder and rectal walls: adenocarcinoma of the prostate. Cancer Radiother. 2011;15:270-8.
17. Mak RH, Hunt D, Efstathiou JA, Heney NM, Jones CU, Lukka HR, et al. Acute and late urinary toxicity following radiation in men with an intact prostate gland or after a radical prostatectomy: a secondary analysis of RTOG 94-08 and 96-01. Urol Oncol. 2016;34:430.e1-7.
18. Ohri N, Dicker AP, Showalter TN. Late toxicity rates following definitive radiotherapy for prostate cancer. Can J Urol. 2012;19:6373-80.
19. Health USDo, Services H, Health NIo, Institute NC. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Bethesda, MD: National Cancer Institute; 2017.
20. Braide K, Kindblom J, Lindencrona U, Månsson M, Hugosson J. The value of a bladder-filling protocol for patients with prostate cancer who receive post-operative radiation: results from a prospective clinical trial. Acta Oncol. 2019;58:463-8.
21. Chetiyawardana G, Hoskin PJ, Tsang YM. The implementa-

tion of an empty bladder filling protocol for localised prostate volumetric modulated arctherapy (VMAT): early results of a single institution service evaluation. Br J Radiol. 2020;93: 20200548.
22. Rades D, Küter JD, von Staden M, Al-Salool A, Ziemann C, Janssen S, et al. Evaluation of Reminder App for Optimization of Bladder Filling Status During Hypo-Fractionated Irradiation for Prostate Cancer: Protocol of REFILL-PAC-HYPO Trial. Clin Pract. 2025;15.
23. Huang S, Li T, Guo Y, Mai X, Dai X, Wu M, et al. Impact of bladder volume and bladder shape on radiotherapy consistency and treatment interruption in prostate cancer patients. J Appl Clin Med Phys. 2025;26:e70026.
24. Chen Z, Yang Z, Wang J, Hu W. Dosimetric impact of different bladder and rectum filling during prostate cancer radiotherapy. Radiat Oncol. 2016;11:103.
25. Heng SP, Low SH, Sivamany K. The influence of the bowel and bladder preparation protocol for radiotherapy of prostate cancer using kilo-voltage cone beam CT: our experience. Indian J Cancer. 2015;52:639-44.
26. Chauhan K, Ebner DK, Tzou K, Ryan K, May J, Kaleem T, et al. Assessment of bladder filling during prostate cancer radiation therapy with ultrasound and cone-beam CT. Front Oncol. 2023;13:1200270.
27. Bodusz D, Brajczewska-Bello J, Rutkowski T, Kołosza Z, Cortez AJ, Szymala-Cortez M, et al. The role of ultrasound-based monitoring of bladder volume in patients with prostate cancer during CyberKnife stereotactic radiosurgery. Appl Sci. 2024;14:9091.
28. Reilly MP, Ariani R, Thio E, Roh D, Timoteo M, Cen S, et al. Daily ultrasound imaging for patients undergoing post-prostatectomy radiotherapy predicts and ensures bladder and rectum dosimetric endpoints. Int J Radiat Oncol Biol Phys. 2020;108:e921.
29. Tetar SU, Bruynzeel AME, Lagerwaard FJ, Slotman BJ, Bohoudi O, Palacios MA. Clinical implementation of magnetic resonance imaging guided adaptive radiotherapy for localized prostate cancer. Phys Imaging Radiat Oncol. 2019;9:69-76.
30. Parkinson C, Matthams C, Foley K, Spezi E. Artificial intelligence in radiation oncology: a review of its current status and potential application for the radiotherapy workforce. Radiography (Lond). 2021;27(Suppl 1):S63-8.