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REVIEW ARTICLE

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Can radiation-induced lower urinary tract disease be ameliorated in patients treated for pelvic organ cancer: ICI-RS 2019?

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Abstract

Aims: This article reviews the clinical outcomes and basic science related to negative effects of radiotherapy (RT) on the lower urinary tract (LUT) when used to treat pelvic malignancies.

Methods: The topic was discussed at the 2019 meeting of the International Consultation on Incontinence—Research Society during a "think tank" session and is summarized in the present article.

Results: RT is associated with adverse effects on the LUT, which may occur during treatment or which can develop over decades posttreatment. Here, we summarize the incidence and extent of clinical symptoms associated with several modes of delivery of RT. RT impact on normal tissues including urethra, bladder, and ureters is discussed, and the underlying biology is examined. We discuss innovative in vivo methodologies to mimic RT in the laboratory and their potential use in the elucidation of mechanisms underlying radiation-associated pathophysiology. Finally, emerging questions that need to be addressed through further research are proposed.

Conclusions: We conclude that RT-induced negative effects on the LUT represent a significant clinical problem. Although this has been reduced with improved methods of delivery to spare normal tissue, we need to (a) discover better approaches to protect normal tissue and (b) develop effective treatments to reverse radiation damage.

KEYWORDS

brachytherapy, external beam radiation therapy, hemorrhagic cystitis, lower urinary tract fibrosis, pelvic floor muscle damage, prevention of radiation-induced LUT complications, radiation cystitis

1 | INTRODUCTION

The negative effects of radiotherapy (RT) on lower urinary tract (LUT) function predominantly present as stricture, contraction or obstruction, (hemorrhagic) inflammation, impaired pelvic floor muscle function or detrusor overactivity. These complications are not uncommon and increase with time. When they occur, they are often more difficult to treat than postsurgical side-effects and when treated they often have further complications. In this International Consultation on Incontinence—Research Society (ICI-RS) 2019 Think Tank we explored the prevalence, impact, and pathophysiology of radiation-induced effects on the LUT. We also explored possible preventive measures and treatment options. Finally, we identified gaps in knowledge about this issue.

2 | RT RELATED UROLOGICAL COMPLICATIONS—THE EXTENT OF THE PROBLEM

2.1 | Bladder complications

Treatment of pelvic malignancy with RT can cause bladder, prostate, and bowel complications. Bladder complications seem to develop at a steady pace for up to 25 years after RT. They occur in 28% of women who have had external beam radiotherapy (EBRT) ± brachytherapy (BT) for cervical cancer by 5 years posttreatment, although 61% to 81% resolved with conservative management.[1] In 32 465 men having radical prostatectomy (RP) or RT for prostate cancer (PC), the 5-year cumulative incidence of readmission for treatment-related complications was 17.5% and 27.1%, respectively. Men post-RT had the highest 5-yr cumulative incidence of open surgical procedures (1.1% vs 0.8%). The cumulative incidence of secondary malignancies 5 to 9 years after RT was also higher (4.5% vs 1.8%).[2] In men surviving 10 years following EBRT or BT for PC, grade 2 and 3 urological adverse effects (RT common toxicity criteria) occurred in 7% to 19% and 5% to 13%, respectively.[3]

2.2 | Urethral complications

Urethral strictures are a predominantly male problem and have a pooled estimate prevalence at 4 years of 1.5% after EBRT, 1.9% after BT, and 4.9% after BT plus EBRT.[4] Although post-RT urethral strictures can be managed definitively with urethroplasty, there are higher recurrence rates at 5% to 30% following anastomotic urethroplasty and 22% to 29% following buccal mucosal graft substitution urethroplasty. Urinary incontinence, while rarely noted after urethroplasty in general, occurs in up to 44% following urethroplasty for post-RT strictures.[5]

2.3 | Urethral sphincter damage

Patient-reported urinary incontinence occurs in up to 12% of men having RT alone for PC and in up to 52% of men having RT following RP for PC.[6] Success rates are inferior for male slings in post-RT cohorts with 52.5% continence vs 63.2% in nonirradiated men at 12 months. Complication rates are higher with infection and explantation rates at 8.3% vs 4.8% in nonirradiated men.[7]

In men having artificial urinary sphincter insertion for stress urinary incontinence (SUI) following RP with or without RT, those post-RT have significantly higher rates of explantation (27% vs 7% at 5 years), erosion (18% vs 7% at 5 years), infection (21% vs 6% at 5 years), and significantly worse continence outcomes (74% vs 85% at 5 years).[8,9] Similarly, RT has been associated with worse continence outcomes (40% vs 78%) and increased erosion and explantation rates (60% vs 26%) in women having artificial urinary sphincter implant.[10]

2.4 | Distal ureter damage

Distal ureteric stricture or obstruction occurs in 6% of men after PC RT[11] and in 10.3% of women after RT for cervical cancer.[12] Treatment is often complex due to associated bladder dysfunction in 56%. There is significant associated morbidity of surgical treatment with complications in 17% and re-intervention in 27%.[13]

2.5 | Pelvic floor muscles

One retrospective study of 108 men with PC who underwent MRI before and after EBRT or BT showed significant reduction of urethral length and increased signal intensity (suggestive of fibrotic changes) of the obturator internus muscle and periurethral part of the levator ani.[14]

A systematic review including 13 studies with 692 patients after multiple RT protocols, concluded that, in a population of men treated with EBRT and/or BT for PC, there was level 2B evidence that RT affected the structure of the pelvic floor muscles (PFMs), between 2 and 62 months after radiation.[15] There is level 1B evidence of adverse RT effects on PFM function, mainly activity and contractile response during a maximal voluntary contraction when measured by electromyography.[16]

The severity of muscle tissue damage and its relationship with type/dosage of radiation remains unclear.

2.6 | Effects of RT on the lower urinary tract, measured by urodynamics

A significant reduction in maximum cystometric capacity (MCC) has been observed after RT for PC. The reduction in MCC is more pronounced supine than upright and there are also reductions in the volume at the first sensation and normal desire to void.[17] In the longer term, compliance is reduced by a factor of 3.5 and the incidence of SUI increases by a factor of 9.3.[18] Similarly, women following RT for cervical cancer have a significant reduction in volume at the first sensation, MCC, maximum urethral closure pressure, and functional urethral length at 5 to 11 years post-RT. They also have a significant increase in mean detrusor filling pressure and incidence of detrusor overactivity.[19]

3 | CELLULAR AND MOLECULAR BIOLOGY BACKGROUND OF RT-INDUCED CHANGES IN THE LOWER URINARY TRACT

3.1 | Radiation effects on cells and tissue

Ionizing radiation (α-particles, β-particles, X-rays, γ-rays) impacts cells, tissues, organs, and individuals over a period of time from milliseconds to years following radiation therapy. In brief, radiation interacts with the aqueous components of cells generating reactive oxygen species (ROS) including hydroxyl radicals (^{-}OH), ionized water (H_2O^{+}), superoxide (O_2^{-}), and hydrogen peroxide (H_2O_2) and reactive nitrogen species. These induce cellular damage, particularly double-strand breaks (DSBs) in DNA that are typically unrepaired in cancer cells, leading to cell death (the underpinning mechanism of radiation therapy) but are more likely to be repaired in normal cells. Following radiation, release of cytokines and activation of inflammatory signaling pathways including cyclooxygenase-2 amplifies radiation damage.[20] With RT, collateral damage is unavoidable in organs adjacent to the tumor, but damage is more likely to be repaired in normal cells.

3.2 | Radiation-induced bystander effects

Radiation is also associated with radiation-induced bystander effects, defined as cells responding to their neighbors having been irradiated.[21] Radiation-induced bystander effects are mediated in a number of ways including the release of signaling molecules from irradiated cells that effect neighboring cells in a paracrine fashion in addition to autocrine effects, and/or intercellular communication via gap junctions. Bystander effects can synergize the direct effects of irradiation, promoting cell death in tumor cells; however, they can also contribute to normal cell toxicity through activation of inflammatory signaling or proapoptotic signaling.

3.3 | Mechanisms of radiation-induced bladder toxicity

Radiation-induced bladder toxicity is defined as (a) early inflammation/radiation (sometimes hemorrhagic) cystitis, which resolves in many patients and (b) late fibrosis with filling/voiding dysfunction occurring months or years later. Early inflammation is triggered seconds-to-hours following radiation and is associated with activation of transforming growth factor beta signaling, generation of ROS, DNA damage-repair (or mis-repair), cell death, and activation of chemokine signaling cascades. Inflammatory cells, including macrophages, accumulate in irradiated tissues which also display edema. Tissue remodeling is triggered and over months to years, collagen synthesis and deposition along with excessive extracellular matrix occurs, bringing about fibrosis and bladder dysfunction.[22]

3.4 | Radiation and the urothelium

Direct irradiation of human urothelial cells induces DNA DSBs and reduces cell survival.[23] Radiation-induced bystander effects were observed in experiments where half of a cell flask was irradiated and the other half shielded. Cells under the shield had significantly more DSBs than nonirradiated cells, suggesting that irradiated urothelial cells released signaling molecules into the media that affected the neighboring cells.[23]

In vivo irradiation experiments show early patchy loss of the urothelium after irradiation and subsequent hyperplasia.[24]

3.5 | Radiation and the detrusor

The bladder has two contraction modalities; large coordinated neurogenic contractions during voiding and small nonvoiding contractions during filling. Tension recording studies across several species where ex vivo

bladder tissue has been irradiated, or animals have been irradiated in vivo and bladders studied post-sacrifice, demonstrate that irradiation does not directly impact the ability of the detrusor smooth muscle to contract (guinea-pig[25] and rat[26]). However, nerve-evoked contractions via electrical field stimulation were significantly smaller in irradiated bladder tissue. Interestingly, when similar experiments were carried out on denuded, mucosa-free strips, nerve-evoked contractions were little affected by irradiation.[25]

Giglio et al[26] reported that nerve-evoked contractions in bladder tissue from irradiated animals (several weeks postirradiation) were not only smaller but had higher purinergic and lower cholinergic components.[27] In bladder tissue from irradiated animals, contractions evoked by carbachol or alpha,beta-methyleneadenosine 5′-triphosphate lithium salt were smaller than in controls. This suggests differences in receptor-mediated signaling given that the ability of the smooth muscle to contract was not affected.[26] In the longer term, these protocols evoke fibrosis of the bladder lamina propria.[28]

3.6 | Clinically relevant in vivo studies

The recent development of small animal radiation research platforms (SARRPs) mimics the clinical environment where radiation is delivered to the bladder through multiple beams under computed tomography image guidance. SARRP-irradiated rodent bladders exhibit edema, inflammatory cell infiltrate, blood vessel dilation, and urothelial loss/hyperplasia. These bladders develop fibrosis and disruption of the urothelial barrier[24] and therefore represent a promising clinically relevant model for research.

Recently, relaxin, a peptide hormone that acts via relaxin family peptide receptors RXFP1, RXFP2, and RXFP3 and signal transduction pathways in normal physiology, was found to prevent chronic radiation cystitis in mice.[29] Relaxin/RXFP1 signaling contributes to organ protection through anti-fibrotic and anti-inflammatory mechanisms.[30] Relaxin is produced by the corpus luteum, uterus and placenta in females and is classically known for its role in extracellular matrix remodeling in pregnancy-related tissues. In males, it is produced by the prostate and relaxin's important anti-fibrotic role in the bladder, kidney, skin, lung, and heart is now well established.[31] Histological assessment of bladder tissue from mice pretreated with relaxin before irradiation showed less fibrosis, decreased collagen content, improved bladder wall architecture, increased detrusor contractility, and improved compliance compared with irradiated control.[29]

4 | FACTORS THAT MODULATE THE EFFECT OF RADIOTHERAPY ON LOWER URINARY TRACT FUNCTION

Neo-adjuvant chemotherapy has been associated with an increase of adverse LUT outcomes in chemoradiation for carcinoma of the cervix uteri and chemoradiation for anal carcinoma.[32]

In PC treatment, neo-adjuvant androgen deprivation therapy (ADT) with BT as well as adjuvant ADT with EBRT is given to subgroups of men. Neo-adjuvant ADT is given to BT candidates who have prostates greater than 50 cm^3 hindering planned radioactive seed placement. However, patients who achieved smaller prostate volumes (median 30%) through the use of ADT maintained a significantly elevated risk (threefold: 27% vs 9%) for obstructive urinary complications, commensurate with their initially large prostate volume.[33] Furthermore, hormonally manipulated patients were more likely to undergo post-implant surgical intervention (transurethral resection of the prostate) than hormone naive patients (5.2% vs 0.3%, $P = .001$).[34]

In men treated with EBRT for high-risk PC, adjuvant ADT improves the oncological outcome; this has been shown in an randomized controlled trial (RCT) comparing 6 months vs 3 years of adjuvant ADT after EBRT. Unfortunately, in the 3 years group, there were more grade 2 LUT complications, than in the 6 months group.[35]

5 | HOW CAN THE EFFECT OF RT-INDUCED LUT DISEASE BE AMELIORATED?

In the treatment of localized/locally advanced PC, RT has evolved from simple treatment fields to three-dimensional (3D) conformal radiation therapy (CRT). However, the improved disease control was achieved at the expense of increased toxicity, and this provided the impetus for intensity-modulated radiotherapy (IMRT) which creates dynamic fields that vary in intensity across their cross-section. Studies have demonstrated that IMRT results in fewer toxicities than 3D-CRT.[36,37]

There is increasing evidence that PC is particularly sensitive to radiation delivered at a high dose per fraction reflected by a low alpha-beta ratio (a/b ratio). The a/b ratio for PC is believed to be around 1.4 to 1.8.[38] This is even lower than the typical a/b ratio of late effects in normal tissue (around 3) and much lower than the a/b ratio of acutely reacting normal tissues (around 10). This lends itself to the potential for better outcomes with high

dose per fraction EBRT (hypofractionated regimes) or high-dose-rate BT than with conventional treatments (EBRT using 2 Gy per fraction which represents "normal/conventional" fractionation) with a reduction in late sequelae.[39]

Studies investigating moderate hypofractionation (2.4-4 Gy/#) have shown comparable outcomes to conventional fractionation without worsening genitourinary (GU) and gastrointestinal (GI) toxicities.[40-43] The CHHiP trial reported 5-year outcomes and the hypofractionated schedule (60 Gy in 20 sessions) was not inferior to the 74 Gy schedule. These studies however were associated with a slight increase in late GU toxicity. Extreme hypofractionation (≥5 Gy/#) is made possible with stereotactic RT. A meta-analysis with over 6000 patients treated in prospective studies demonstrates the efficacy of extreme hypofractionation.[44] The HYPO-RT-PC trial showed that a schedule of 7 fractions of 6.1 Gy delivered every other day over 2.5 weeks was noninferior in terms of failure-free survival compared with conventional fractionation of 78 Gy over 8 weeks (2 Gy per fraction), with similar proportions of late toxicity in each group.[45] The PACE trial confirmed that extreme hypofractionation with stereotactic body RT does not increase either acute GI or GU toxicity.[46]

Image-guided radiotherapy (IGRT) encompasses techniques for localizing the target: by localizing surrogates[47] or anatomical features.[48] IGRT improves the accuracy of treatment delivery, allowing for dose escalation with an improved GU and GI toxicity profile.[49]

Another factor influencing RT toxicity is the proximity of prostate and rectum. A hydrogel spacer that moves the rectum away from the prostate showed significantly less rectal and bladder toxicity.[50]

Prostate BT is targeted directly at the prostate gland via a radiation source that is implanted or temporarily placed within the gland. This allows safe dose escalation to the prostate and results in a reduction in the dose to the bladder and rectum, thus reducing the incidence of urinary and sexual function side-effects compared with surgery, and a lower incidence of bowel side-effects than EBRT.[51]

6 | MANAGEMENT OPTIONS FOR RT-INDUCED LUT DISEASE

The best way to decrease the burden of radiation-induced LUT disease is by prevention through pretreatment patient selection. Chen et al[52] demonstrated that 36 months urinary incontinence rates after RT for PC were much lower in men who had no baseline LUT symptoms in comparison to those who had at least 1 "distressful" LUT symptom. For BT, the rates were 17% and 50% (2.9-fold increase) and for EBRT the corresponding rates of incontinence were 18% vs 74% (4.1-fold increase).

Once established, LUT disease often becomes a chronic problem and is notoriously difficult to treat. To date, there is still no solid evidence for a significant benefit of any medical treatment option. In special situations like hemorrhagic radiation-induced cystitis, transfusion, formalin, alum, fulguration, and finally hyperbaric oxygen, have been tried. Botulinum toxin A (BTX-A) is used in patients with an overactive bladder not responding to oral medication. In some particularly refractory cases, cystoplasty or urinary diversion may be a last resort. However, there is a lack of high-quality research for these treatments, and hence each patient is treated empirically.

Chronic post-radiation LUT disease may be associated with hemorrhagic cystitis. Hyperbaric oxygen therapy increases dissolved oxygen in serum, leading to a reversal of ischemia in "lethal corners" of the bladder far from existing blood vessels.[53,54] Such tissue reoxygenation leads to neovascularization and growth of healthy granulation tissue.[49,50] Weiss et al[53] showed that hyperoxia of tissue resulting from breathing 100% oxygen at 2 bar for 2 hours daily over the course of 6 to 8 weeks (mean of 33 sessions) caused cessation of hematuria and bladder preservation in 12/13 of patients so treated (mean follow-up of 2.5 years). Bevers et al[54] reported the results of a prospective study of hyperbaric oxygen (20 sessions of 90 minutes at 3 bar with 100% oxygen inhalation in a multiplace hyperbaric chamber) in 40 patients with biopsy-proven radiation cystitis and severe hematuria. Hematuria disappeared completely or improved in 37 patients. The mean follow-up was 23.1 months (range 1-74), and the recurrence rate was 0.12/year. Whether hyperbaric oxygen therapy may be useful as a primary or adjunctive treatment for radiation-induced lower urinary tract symptoms (LUTS) might be the target of future study. Ideally, such a study should be an (expensive) RCT comparing active with sham hyperbaric chamber treatment. And, at which level of LUTS severity should patients be randomized?

The responses to BTX-A treatment in patients with idiopathic and neuropathic detrusor overactivity are well documented. However, the literature on BTX-A in patients who have had prior pelvic RT is sparse. A series of 49 patients treated over a 10-year period was recently reported.[55] Patients were separated by urodynamics into categories; loss of compliance alone, loss of compliance with detrusor overactivity, and early or late detrusor overactivity with normal compliance. Overall, 46% had a clinical response sufficient to justify continued injections. However, the data split clearly into two groups. Patients

with poorly compliant bladders had a 21% response rate and the majority required surgical intervention (cystoplasty or urinary diversion). Patients with detrusor overactivity but preserved bladder capacity responded much better with 75% continuing to be managed with Botox alone. It therefore seems that poor bladder compliance due to replacement of muscle by fibrosis, is a predictor of BTX-A failure.

7 | RESEARCH QUESTIONS

Several questions have emerged that need to be addressed by further research:

(1) Does early radiation-induced urothelium pathology drive long-term physiological changes? (SARRP)
(2) Does the radiation-induced inflammatory microenvironment evoke fibrosis and remodeling? (SARRP)
(3) Can relaxin prevent acute radiation-induced inflammation and fibrosis in a clinical setting? Is the time ripe for a phase 1 trial in humans?
(4) If acute radiation-induced inflammation can be alleviated and fibrosis prevented, for example by relaxin, can the therapeutic dose of radiation in cancer treatment be increased and health-related quality of life maintained?
(5) MRI studies (before and after in the same patient) with high methodological quality are needed to increase the level of evidence of the finding of radiation-induced adverse effects on PFMs.

8 | SUMMARY

Severe LUTD can develop as a chronic problem, often many years after the exposure to RT. Radiation alters bladder contractility through a poorly understood effect on the integrity of mucosal-detrusor communication. Urothelial cells are radiosensitive, exhibiting both direct and bystander responses to irradiation. Moreover, the bladder wall experiences inflammation and undergoes remodeling and fibrosis after radiation. In mice subjected to in vivo radiation, relaxin treatment prevented fibrosis and normalized bladder activity.

Optimized patient selection before RT might help to decrease the prevalence of radiation-induced LUTD: one has to assess baseline urinary tract symptoms and signs with validated questionnaires! On the other hand, LUT problems may be worsened by (neo-)adjuvant chemotherapy or ADT.

Improving radiation techniques and delivery may help to decrease the adverse effects.

Management of these problems once they have been established remains a difficult issue: conservative and minimally invasive treatment options are moderately effective at best. Surgical therapies, such as functional reconstruction and prosthetics, have worse outcomes and more complications after RT. Hence, prevention of RT side-effects remains the current priority in patient care.

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REFERENCES

1. Georg P, Boni A, Ghabuous A, et al. Time course of late rectal- and urinary bladder side effects after MRI-guided adaptive brachytherapy for cervical cancer. *Strahlenther Onkol*. 2013;189:535-540.
2. Nam RK, Cheung P, Herschorn S, et al. Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study. *Lancet Oncol*. 2014;15:223-231.
3. Lawton CA, Won M, Pilepich MV, et al. Long-term treatment sequelae following external beam irradiation for adenocarcinoma of the prostate: analysis of RTOG studies 7506 and 7706. *Int J Radiat Oncol Biol Phys*. 1991;21:935-939.
4. Awad MA, Gaither TW, Osterberg EC, Murphy GP, Baradaran N, Breyer BN. Prostate cancer radiation and urethral strictures: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis*. 2018;21:168-174.
5. Chung PH, Esposito P, Wessells H, Voelzke BB. Incidence of stress urinary incontinence after posterior urethroplasty for radiation-induced urethral strictures. *Urology*. 2018;114:188-192.
6. Daugherty M, Chelluri R, Bratslavsky G, Byler T. Are we underestimating the rates of incontinence after prostate cancer treatment? Results from NHANES. *Int Urol Nephrol*. 2017;49:1715-1721.
7. Spie R, Claudon P, Raynal G, Saint F, Petit J. Radiotherapy influence, about results of the InVance(®) male sling in men with stress urinary incontinence. *Prog Urol*. 2011;21:549-553.
8. Ravier E, Fassi-Fehri H, Crouzet S, Gelet A, Abid N, Martin X. Complications of artificial urinary sphincter implantation in patients with or without prior radiotherapy. *BJU Int*. 2015;115:300-307.
9. Bates A, Martin RM, Terry T. Complications following artificial urinary sphincter placement after radical prostatectomy and radiotherapy: a meta-analysis. *BJU Int*. 2015;116:623-633.
10. Vayleux B, Rigaud J, Branchereau J, et al. Pelvic radiotherapy and artificial urinary sphincter in women. *Prog Urol*. 2012;22:534-539.

11. Elliott SP, Malaeb BS. Long-term adverse effects of pelvic radiotherapy. *World J Urol*. 2011;29:35-41.
12. McIntyre JE, Eifel PJ, Levenback C, Oswald MJ. Ureteral stricture as a late complication of radiotherapy for stage 1B carcinoma of the uterine cervix. *Cancer*. 1995;1:836-843.
13. Toia B, Seth J, Ecclestone H, et al. Outcomes of reconstructive surgery after pelvic radiotherapy. *Scand J Urol*. 2019;53(2-3): 156-160.
14. Marigliano C, Donati OF, Vargas HA, et al. MRI findings of radiation-induced changes in the urethra and periurethral tissues after treatment for prostate cancer. *Eur J Radiol*. 2013;82: e775-e781.
15. Bernard S, Ouellet MP, Moffet H, Roy JS, Dumoulin C. Effects of radiation therapy on the structure and function of the pelvic floor muscles of patients with cancer in the pelvic area: a systematic review. *J Cancer Surviv*. 2016;10:351-362.
16. Dieperink KB, Johansen C, Hansen S, et al. The effects of multidisciplinary rehabilitation: RePCa—a randomised study among primary prostate cancer patients. *Br J Cancer*. 2013;109: 3005-3013.
17. Choo R, Do V, Herschorn S, et al. Urodynamic changes at 18 months post-therapy in patients treated with external beam radiotherapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys*. 2002;53:290-296.
18. Mendez-Rubio S, Salinas-Casado J, Virseda-Chamorro M, Esteban-Fuertes M, Menendez-Sanchez P, Moreno-Sierra J. Long-term adverse effects on bladder filling phase in males submitted to the pelvic radiotherapy. *Arch Esp Urol*. 2015;68: 609-614.
19. Parkin DE, Davis JA, Symonds RP. Urodynamic findings following radiotherapy for cervical carcinoma. *Br J Urol*. 1988;61: 213-217.
20. Cheki M, Yahyapour R, Farhood B, et al. COX-2 in radiotherapy: a potential target for radioprotection and radiosensitization. *Curr Mol Pharmacol*. 2018;11(3):173-183.
21. Prise KM, O'Sullivan JM. Radiation-induced bystander signalling in cancer therapy. *Nat Rev Cancer*. 2009;9(5):351-360.
22. Bentzen SM. Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. *Nat Rev Cancer*. 2006;6(9):702-713.
23. Bill MA, Srivastava K, Breen C, et al. Dual effects of radiation bystander signaling in urothelial cancer: purinergic-activation of apoptosis attenuates survival of urothelial cancer and normal urothelial cells. *Oncotarget*. 2017;8(57):97331-97343.
24. Zwaans BM, Krueger S, Bartolone SN, Chancellor MB, Marples B, Lamb LE. Modeling of chronic radiation-induced cystitis in mice. *Adv Radiat Oncol*. 2016;1(4):333-343.
25. McDonnell BM, Buchanan PJ, Prise KM, McCloskey KD. Acute radiation impacts contractility of guinea-pig bladder strips affecting mucosal-detrusor interactions. *PLOS One*. 2018;13(3): e0193923.
26. Giglio D, Podmolikova L, Tobin G. Changes in the neuronal control of the urinary bladder in a model of radiation cystitis. *J Pharmacol Exp Ther*. 2018;365(2):327-335.
27. Sun Y, Chai TC. Role of purinergic signaling in voiding dysfunction. *Curr Bladder Dysfunct Rep*. 2010;5(4):219-224.
28. Andersson KE, McCloskey KD. Lamina propria: the functional center of the bladder? *Neurourol Urodyn*. 2014;33(1):9-16.
29. Ikeda Y, Zabbarova IV, Birder LA, et al. Relaxin-2 therapy reverses radiation-induced fibrosis and restores bladder function in mice. *Neurourol Urodyn*. 2018;37(8):2441-2451.
30. Valkovic AL, Bathgate Ross AD, Samuel CS, Kocana M. Understanding relaxin signalling at the cellular level. *Mol Cell Endocrinol*. 2019;487(1 May):24-33.
31. Kanai AJ, Konieczko EM, Bennettde RG, Samuel CS, Royce SG. Relaxin and fibrosis: emerging targets, challenges, and future directions. *Mol Cell Endocrinol*. 2019;487:66-74.
32. Zou W, Han Y, Zhang Y, et al. Neoadjuvant chemotherapy plus surgery versus concurrent chemoradiation in stage IB2-IIB cervical cancer: a systematic review and meta-analysis. *PLOS One*. 2019;14(11):e0225264.
33. Petit JH, Gluck C, Kiger WS 3rd, et al. Androgen deprivation-mediated cytoreduction before interstitial brachytherapy for prostate cancer does not abrogate the elevated risk of urinary morbidity associated with larger initial prostate volume. *Brachytherapy*. 2007;6(4):267-271.
34. Hinerman-Mulroy A, Merrick GS, Butler WM, Wallner KE, Allen Z, Adamovich E. Androgen deprivation-induced changes in prostate anatomy predict urinary morbidity after permanent interstitial brachytherapy. *Int J Radiat Oncol Biol Phys*. 2004;59: 1367-1382.
35. Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med*. 2009;360:2516-2527.
36. Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2008;70(4): 1124-1129.
37. Michalski JM, Y. Yan Y, Watkins-Bruner D, et al. Preliminary toxicity analysis of 3-dimensional conformal radiation therapy versus intensity modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group 0126 prostate cancer trial. *Int J Radiat Oncol Biol Phys*. 2013;87(5):932-938.
38. Leborgne F, Fowler J, Leborgne JH, Mezzera J. Later outcomes and alpha/beta estimate from hypofractionated conformal three-dimensional radiotherapy versus standard fractionation for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2012; 82(3):1200-1207.
39. Fowler JF, Ritter MA, Chappell RJ, Brenner DJ. What hypofractionated protocols should be tested for prostate cancer? *Int J Radiat Oncol Biol Phys*. 2003;56(4):1093-1104.
40. Aluwini S, Pos F, Schimmel E, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): late toxicity results from a randomised, non-inferiority, phase 3 trial. *Lancet Oncol*. 2016;17(4): 464-474.
41. Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol*. 2016;17(8): 1047-1060.
42. Lee WR, Dignam JJ, Amin MB, et al. Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. *J Clin Oncol*. 2016;34(20):2325-2332.

43. Catton CN, Lukka H, Gu CS, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. *J Clin Oncol*. 2017;35(17):1884-1890.
44. Jackson WC, J. Silva J. Stereotactic body radiation therapy for localized prostate cancer: a systematic review and meta-analysis of over 6,000 patients treated on prospective studies. *Int J Radiat Oncol Biol Phys*. 2019;104(4):778-789.
45. Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet*. 2019;394(10196):385-395.
46. Brand DH, Tree AC, Ostler P, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol*. 2019;20(11):1531-1543.
47. Challapalli A, Jones E, Harvey C, Hellawell GO, Mangar SA. High dose rate prostate brachytherapy: an overview of the rationale, experience and emerging applications in the treatment of prostate cancer. *Br J Radiol*. 2012;85(Spec No 1):S18-S27.
48. Hilman S, Smith R, Masson S, et al. Implementation of a daily transperineal ultrasound system as image-guided radiotherapy for prostate cancer. *Clin Oncol (R Coll Radiol)*. 2017;29(1):e49.
49. Verellen D, De Ridder M, Linthout N, Tournel K, Soete G, Storme G. Innovations in image-guided radiotherapy. *Nat Rev Cancer*. 2007;7(12):949-960.
50. Hamstra DA, Mariados N, Sylvester J, et al. Continued benefit to rectal separation for prostate radiation therapy: final results of a phase III trial. *Int J Radiat Oncol Biol Phys*. 2017;97(5):976-985.
51. Ferrer M, Suarez JF, Guedea F, et al. Health-related quality of life 2 years after treatment with radical prostatectomy, prostate brachytherapy, or external beam radiotherapy in patients with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2008;72(2):421-432.
52. Chen RC, Clark JA, Talcott JA. Individualizing quality-of-life outcomes reporting: how localized prostate cancer treatments affect patients with different levels of baseline urinary, bowel and sexual function. *J Clin Oncol*. 2009;27:3916-3922.
53. Weiss JP, Mattei DM, Neville EC, Hanno PM. Primary treatment of radiation-induced hemorrhagic cystitis with hyperbaric oxygen: 10-year experience. *J Urol*. 1994;151:1514-1517.
54. Bevers RF, Bakker DJ, Kurth KH. Hyperbaric oxygen treatment for haemorrhagic radiation cystitis. *Lancet*. 1995;346(8978):803-805.
55. Toia B, Pakzad M, Hamid R, Greenwell T, Ockrim JL. Botulinum toxin A—an effective treatment in patients following radiotherapy? *J Urol*. 2019;201(4S):e1188.

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