REVIEW

Efficacy and Applications of Hydrogel Spacers in Prostate Cancer Radiotherapy: A Clinical Study and Literature Review

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Keywords: Hydrogel Spacers; Radiotherapy; Prostate Cancer; SpaceOAR; Quality of Life; Public Health; Health Management;

ABSTRACT

Introduction: Radiation therapy (RT) is a common treatment for prostate cancer (PCa), but it can cause significant side effects, especially on the patient's quality of life (QoL). Hydrogel spacers, such as SpaceOAR, have been developed to reduce these side effects by creating a barrier between the prostate and the rectum.

Methods: This clinical study and literature review analyzed the efficacy and applications of hydrogel spacers in PCa RT. Randomized and multicenter clinical trials, as well as systematic reviews and meta-analyses were reviewed. Efficacy was measured by the reduction of side effects, especially rectal ulceration, and by the improvement in patients' CT.

Results: The results showed that using hydrogel spacers significantly reduced the incidence of serious side effects, such as rectal ulceration, in patients undergoing RT. In addition, patients who received hydrogel spacers reported improved QT and less discomfort during treatment.

Discussion: It is important to minimize the side effects of RT to improve patients' CT. Hydrogel spacers have shown to be a promising approach, with significant benefits in terms of symptom reduction and improvement in CT. However, further studies are needed to confirm long-term results and to assess the long-term safety of hydrogel use.

Conclusion: Hydrogel spacers represent an important innovation in PCa RT, offering an effective way to reduce side effects and improve patient outcomes. This study suggests that the use of hydrogel spacers should be considered a best practice in PCa RT treatments.

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What do we already know about this topic?
We already know that hydrogel spacers are effective in reducing rectal toxicity during prostate cancer radiotherapy. Clinical studies and meta-analyses have shown that the insertion of hydrogel spacers significantly reduces the radiation dose received by the rectum, reducing adverse side effects and improving patients' quality of life. In addition, the use of hydrogel spacers has shown benefits in radiotherapy dose compliance, especially in three-dimensional conformal radiotherapy (3D-CRT) and stereotactic body radiotherapy (SBRT) treatments. Hydrogel spacers are safe and well tolerated, with a low incidence of serious complications. Studies also indicate that these devices can improve patient outcomes by providing effective protection to adjacent healthy tissues and allowing greater treatment precision. Economic analysis suggests that the use of hydrogel spacers may be cost-effective, considering the reduction of complications and additional treatments.
What is the main contribution to Evidence-Based Practice from this article?
The main contribution of this article to evidence-based practice is the confirmation of the efficacy and safety of hydrogel spacers in prostate cancer radiotherapy. By significantly reducing rectal toxicity, hydrogel spacers improve patients' quality of life, allowing for more precise and safe treatment. This study provides robust data supporting the use of these devices as an effective intervention to protect adjacent healthy tissues during radiotherapy. The comprehensive analysis of clinical studies and literature review consolidate the existing evidence, providing a solid basis for the widespread adoption of hydrogel spacers in clinical practice. In addition, the study highlights the importance of economic evaluation and patient satisfaction, which are crucial aspects for the implementation of new technologies in healthcare.
By gathering and analyzing data from multiple sources, the article contributes to the optimization of radiotherapy techniques and offers practical guidelines for oncologists and radiation oncologists. Thus, it promotes a more informed and evidence-based medical practice, resulting in better outcomes for patients with prostate cancer.
What are this research's implications towards health policy?
This paper on the efficacy and applications of hydrogel spacers in prostate cancer radiotherapy has several important implications for theory, practice, and policy.

Authors' Contributions Statement:
Andrade, Thiago Fostino, lead author, wrote the introduction, methodology and conclusion. Humphreys, Virginia Ribeiro, co-author, wrote the introduction and results. Teixeira, Brendo, co-author, wrote the results and discussion.

Introduction

Worldwide, prostate cancer (PCa) is one of the most common cancers in men. In 2021, 903,500 new cases of PCa were estimated worldwide (INCA, 2023). The estimated number of new cases of PCa in Brazil, for the three years 2023 to 2025, is 71,730, corresponding to an estimated risk of 67.86 new cases per 100,000 men. Excluding non-melanoma skin tumours, PCa ranks second among the most frequent types of cancer (INCA, 2023).
PCa is considered a cancer of the elderly, since around three-quarters of cases worldwide occur after the age of 65. In general, the tumour grows slowly and has a long doubling time, taking around 15 years to reach 1 cm (INCA, 2023).
As the 10-year survival rate for PCa exceeds 80%, most men will survive the disease and are at risk of suffering negative consequences from radiotherapy (RT).
In terms of mortality in Brazil, in 2020, there were 15,841 deaths from PCa, equivalent to a risk of 15.30 deaths per 100,000 men (Brazil, 2023; INCA, 2023).
For the definitive treatment of localized PCa, radical prostatectomy or RT is often recommended. Although both treatment options are considered almost equally effective, side effects are varied. For radical prostatectomy, this includes erectile dysfunction (ED) and incontinence, and for RT, one of the main side effects is rectal toxicity from radiation exposure, due to the proximity of the prostate (Morris et al., 2017).
Furthermore, radiation margins of up to 10 mm around the prostate are necessary due to prostatic movement during treatment to ensure that the entire gland receives the full radiation dose. Due to its anatomic proximity to the sensitive rectal mucosa, the rectum is commonly defined as the dose-limiting

structure for prostate RT. Storey et al. reported that there were significantly more late rectal complications, such as bleeding, when 25% of the rectum received ≥70 Grays (Gy). To overcome this problem, several investigators have evaluated different materials, and injected transperineally, to create space between the prostate and the rectum, including a blood patch, hyaluronic acid, and collagen injections. Although these materials have been shown to reduce the amount of radiation to the rectum, each has certain disadvantages, such as short persistence, degradation during RT, and nonuniform distribution (Morris et al., 2017).
To address some of these drawbacks, a polyethene glycol (PEG)-based hydrogel system (SpaceOAR TM System, Augmenix, Waltham, MA, USA) was developed to temporarily create space between the rectal wall and the prostate during RT, thereby reducing the amount of radiation to the anterior rectum. The hydrogel spacer is a synthetic PEG-based material that is absorbable, water-soluble, nontoxic, and nonimmunogenic. It remains in place for 3 months and then undergoes hydrolysis, liquefies, and is absorbed and eliminated from the body in ~6 months via renal filtration. In situ polymerizing hydrogels have been evaluated as prostate-rectum spacers in cadavers, showing satisfactory hydrogel distribution in all cases. The mean (SD) prostate-rectum separation was 12.8 mm. Overall, a 10-mm prostate-rectum separation was considered sufficient to reduce the mean rectal volume receiving at least 70 Gy (rectal V70) by 83.1% ($P < 0.05$), with no further reduction in rectal V70 at 15-mm separation. Furthermore, hydrogel placement allowed for increased margins of the planning target volume without exceeding rectal dose tolerance (Morris et al., 2017).
Recent technical improvements, such as image-guided intensity-modulated radiation therapy (IG-IMRT), have improved the accuracy and outcomes of prostate radiation delivery. Despite these technological advances, sexual, urinary, and bowel side effects can still occur after IG-IMRT. The rectum, because of its anatomical adjacency to the prostate and its function, is considered an organ at risk in prostate RT and is commonly referred to as a dose-limiting structure.
This anatomic proximity can create trade-offs between adequate prostate dosing and acceptable radiation side effects. The ASCENDE-RT (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiotherapy) trial demonstrated that, compared with men who received 78 Gy external beam radiotherapy (EBRT), men who received brachytherapy (BQT) boost (allowing for significant prostate dose escalation) were twice as likely to be free of biochemical failure at a median follow-up of 6.5 years. However, this increased prostate dose also increased the cumulative rate of grade 3 rectal toxicity from 3.2% to 8.1% (Morris et al., 2017).
Prostate-rectum proximity may also serve as a contraindication to prostate RT in men with certain comorbidities, such as inflammatory bowel disease, vascular disease, or diabetes. Because radiation dose is cumulative, prostate-rectum proximity typically precludes reirradiation in men with localized recurrence after prior RT.
To address the issue of rectal proximity, biomedical spacers have been developed to displace the rectum away from the prostate to minimize rectal radiation injury (Fig. 1). Prada et al published the first results of the prostate-rectum spacer in 2006, in which hyaluronic acid was used to spare the rectum during low-dose-rate brachytherapy (LDB) (Prada et al., 2007). Other materials, including autologous blood, absorbable balloons, collagen, and PEG

hydrogels, have also been evaluated. PEG hydrogel (SpaceOAR System, Augmenix, Inc., Bedford, MA) is the only material systematically studied in a multicenter, randomized, controlled clinical trial.

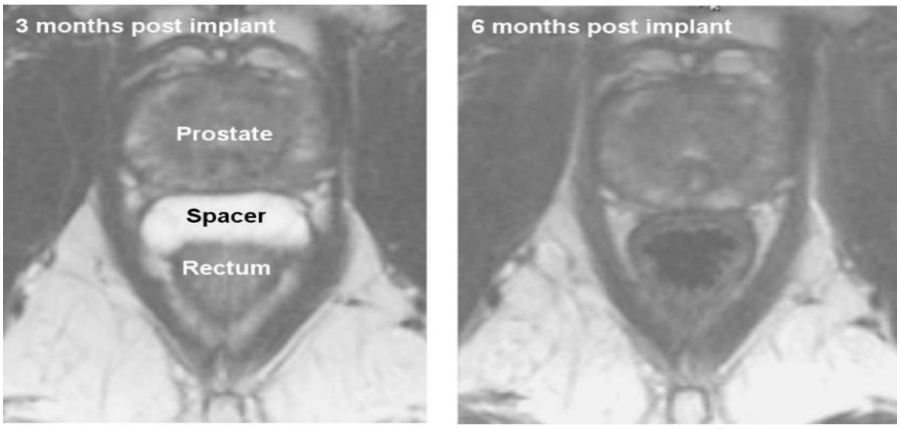


Figure 1 T2-weighted MRI images of a patient with a spacer showing persistence of the hydrogel during completion of RT (left) and absorption 6 months after implantation (right)).

Methodology

This study adopted a mixed design, combining a retrospective clinical analysis with a systematic literature review. The mixed approach will allow a comprehensive understanding of the efficacy and applications of hydrogel spacers in PCa RT. The study population consisted of patients diagnosed with PCa and treated with RT between the years 2010 and 2024.

Patients who used hydrogel spacers during radiotherapy treatment were included. The sample was selected by convenience from the medical records of a hospital specializing in oncology.

Clinical data were collected from patient's medical records, including information on RT dosage, tumour location, use of hydrogel spacers, and clinical outcomes (toxicity, quality of life, tumour control etc.). A systematic literature review was performed using scientific databases (PubMed, Scopus, Cochrane Library etc.). Studies published in the last 20 years addressing the use of hydrogel spacers in RT of PCa will be included.

Clinical data were analyzed using appropriate statistical methods (descriptive analyses, hypothesis testing, logistic regression etc.). Statistical software (R) was used to conduct the analyses. The studies included in the systematic review were analyzed for methodological quality and the main outcomes reported. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) tool was used to guide the review process.

The study was conducted by ethical guidelines for human research. Clinical data were collected anonymously and confidentially. Informed consent was obtained from patients whose data were used in the study. Limitations of the study include the retrospective nature of the clinical analysis and the potential variability in inclusion and treatment criteria between the different studies included in the systematic review.

After the preparation of the bowel and perineal skin, patients were placed in the lithotomy position and anaesthetized with general anaesthesia, conscious sedation, or local anaesthesia. For local anaesthesia, buffered lidocaine (1%–2%) was injected into the perineal skin and along the needle track into the prostate and potential perirectal space. Using transrectal ultrasound guidance, a 15 cm × 18 G needle was advanced through the perineum into Denonvillers' space (fatty tissue posterior to Denonvillers' fascia). Saline was then injected to expand the perirectal space under direct ultrasound visualization. After confirmation of proper needle placement, liquid PEG hydrogel precursors are injected through the applicator, effectively separating the rectum from the prostate. The injected precursors polymerize within 10 seconds to form a soft hydrogel (Fig. 2). The resulting hydrogel spacer is tissue-compatible, immune to radiation damage, maintains its shape for 3 months during RT, and then undergoes hydrolysis, liquefaction, and absorption into the bloodstream, where it is eliminated by renal filtratio.

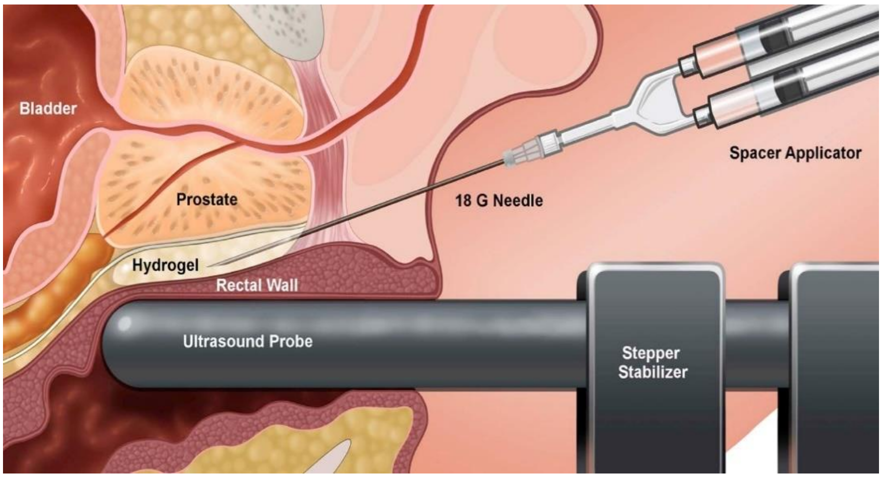


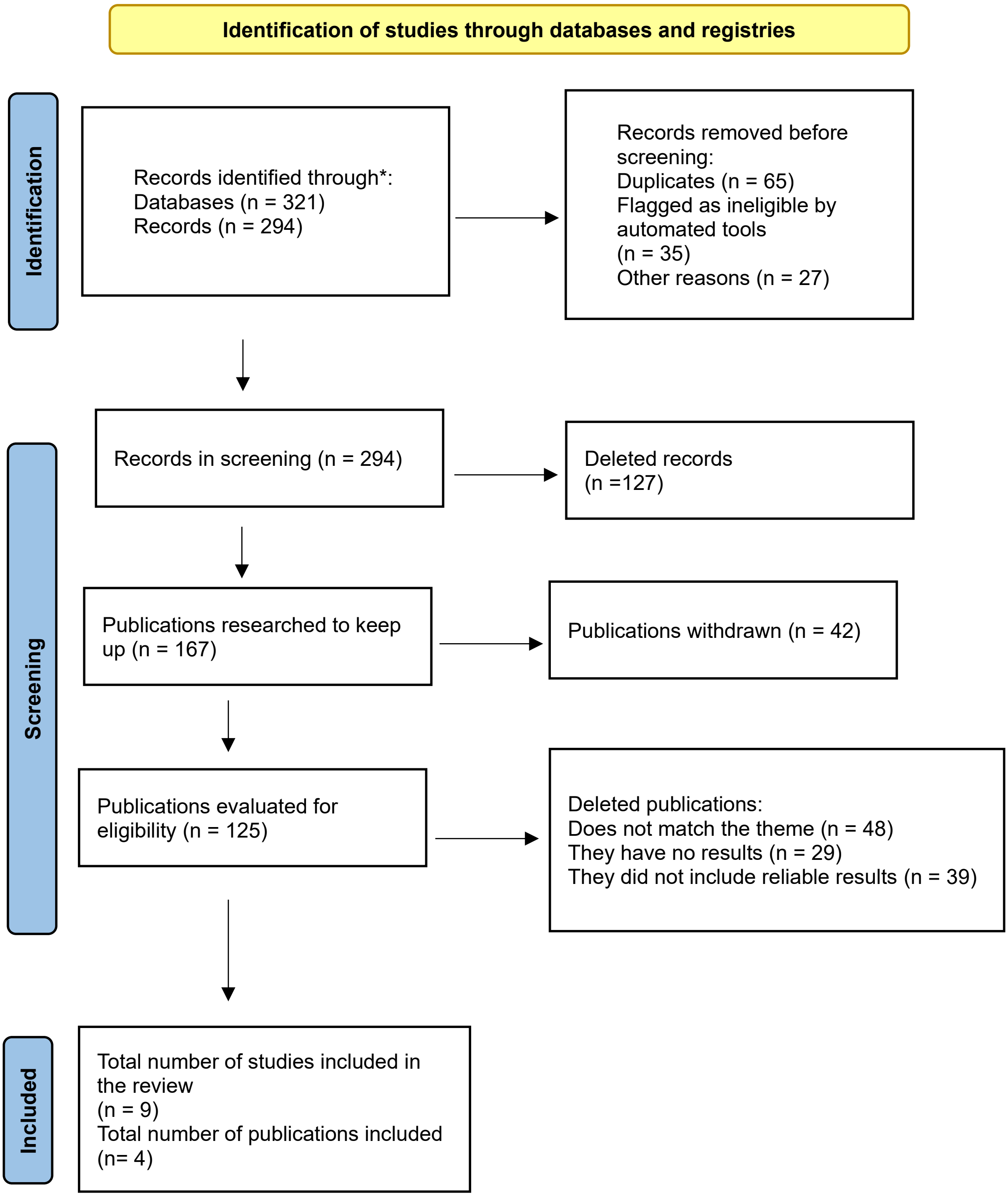
Figure 2: Illustration of transperineal injection of polyethylene glycol hydrogel spacer. The needle is placed at the mid-prostate level between Denonvilliers fascia and the rectal wall, hydrodissection is performed to confirm proper placement, and the hydrogel is injected.

A group of 222 men with low-intermediate risk PCa were randomized 2:1 to hydrogel spacer (n = 149): control (n = 73). The study was conducted in Brazil between 2010 and 2024. Men were blinded to randomization and were not informed of their allocation while in the study. At the same time as spacer placement, fiducial markers were placed for image guidance (Hamstra et al., 2017). Anesthesia was administered at the discretion of the investigator with general anaesthesia (36.4%), local anaesthesia (31.4%), monitored anaesthesia care (25.5%), conscious sedation (5.5%), and other (10.5%).
Within 1 week of the procedure, spacer and control patients underwent computed tomography (CT) and magnetic resonance imaging (MRI) for IG-IMRT dose planning using a prescribed dose of 79.2 Gy in 44 fractions to the prostate ± seminal vesicles. An independent Core Laboratory ensured strict compliance with dose planning protocols, assessed the technical success of the procedure (visibility of hydrogel between the posterior prostatic capsule and the anterior rectal wall on post-implant MRI), and performed all dose and space measurements. All acute (0–3 months) and late (3–37 months) rectal and urinary adverse events were recorded. Adverse events attributed to radiation were scored as toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Additionally, patients completed

the Expanded Prostate Cancer Index Composite (EPIC) health-related quality of life (QOL) questionnaire at baseline and 3, 6, 12, 15, and 37 months. QOL summary scores were assessed for mean changes and changes that met prespecified thresholds for a minimally important difference. For some domains, exploratory analysis of individual items was also performed using previously established thresholds.

Results

PRISMA Flowchart



Radiotherapy and Prostate Cancer (Hypofractionation)

There is an improvement in patient survival with increasing radiation dose in RT for PCa, however, these increases are limited by the maximum dose accepted in organs at risk, such as the bladder, rectum and pelvic bones. The current standard dose for PCa is between 70 Gy and 80 Gy (Brand et al., 2019). This scheme is known as Conventional Fractionation (Gay HA, Michalski, 2018, Arcangeli et al., 2018).

There are two main types of RT for PCa: EBRT and BQT. There are several types of EBRT therapies, some of which are IMRT, image-guided radiotherapy (IGRT), stereotactic radiotherapy (SBRT), and volumetric arc radiotherapy (VMAT).

In recent years, several prospective randomized controlled clinical trials have shown that the use of IMRT (between 2.4 and 3.4 Gy) or ultra-hypofractionated (with fractions > 5 Gy) has comparable efficacy and toxicity to conventional (Brand et al., 2019).

IMRT uses non-uniform radiation beam intensities to target tumors. IGRT is a process that integrates tumour positioning, image guidance tools, and other motion management systems to better direct the radiation beam to the tumour (Brand et al., 2019).

SBRT is a fusion of state-of-the-art tumour imaging with precision radiation treatment delivery systems and provides a complete course of radiation in a shorter period of time and fewer visits when compared to IMRT. On the other hand, BQT is divided into two main forms: BBTD and high-dose brachytherapy (BATD).

Some data suggest that hypofractionation could increase the therapeutic index since PCa cells are especially sensitive to high daily radiation doses (low α-β ratio) (Brand et al., 2019). This radiobiological advantage could translate into future clinical gains. Higher daily doses mean fewer days of treatment.

Moderate and Ultra Hypofractionated Radiotherapy

In RT hypofractionation, there is an increase in the dose per fraction, a decrease in the number of sessions and a moderate reduction in the total dose. This technique is possible because when the α/β ratio of the tumour is the same or lower than that of healthy tissue, a higher dose per fraction combined with a moderate reduction in the total dose may be more effective than using conventional fractionation. The α/β ratio is the dose at which the linear and quadratic components of cell death are equal (Muralidhar et al., 2019).

In hypofractionation, doses above 2 Gy are used and the radiobiological expectation is that there will be a reduction in the therapeutic rate between tumours and a late response in normal tissues. This expectation depends on the α/β ratio for tumour control is considerably higher than for the late response in normal tissues, so hypofractionation may be equal to or even better than conventional fractionation. In order not to reduce the risk of late damage, the total dose is lower when compared to conventional fractionation (Muralidhar et al., 2019).

Rectal Spacers in Polyethylene Glycol Hydrogel (PEG)

BQT is a definitive treatment for PCa. BBTD or BATD can be used alone or in combination with EBRT to treat low-, intermediate-, and high-risk PCa. Dose escalation is strongly associated with reduced biochemical and clinical failure and metastasis-free survival. However, the benefits of dose escalation must be balanced against the risk of increased radiation dose to the bladder, urethra, and particularly the rectum. The higher the radiation dose received by the rectum, the greater the risk of gastrointestinal (GI) toxicity (Muralidhar et al., 2019).

A PEG hydrogel is a hydrophilic polymer that can be crosslinked into a network that can retain a large amount of water. Even minimal increases in the distance between the prostate and the rectum significantly reduce the dose delivered to the rectum due to the rapid dose decay with BQT (Brand et al., 2019).

For EBRT, distancing provides better PTV during EBRT. An average of 1.26 cm of perirectal spacing decreases rectal volume by 73.3% after receiving at least 70 Gy (rV70) (Brand et al., 2019). For BQT where the radiation source is within the prostate, increasing the distance between the prostate and the rectum decreases the radiation dose by the square of the distance. The perirectal space is typically about 2–3 mm thick, and hydrogels can potentially create up to 1.5 cm of separation. Among the various space creation solutions that have been developed (e.g., bioabsorbable balloon, human collagen, hyaluronic acid, and PEG-based hydrogels), hydrogels have the greatest wealth of supporting clinical data and are the most widely used (Mandal and Clegg, 2020).

There is physiological movement of the prostate and rectum between treatment days (interfractional movement) and within the same treatment day (intrafractional movement) that affects the CTV and PTV margins, which may lead to an increase in the dose delivered to healthy tissue and possibly the surrounding OAR (Brand et al., 2019). Hydrogel spacers have been shown to have a significant impact on decreasing prostate motion in both rotational and anteroposterior translational displacements. In addition, it has a positive impact on dampening anteroposterior translational displacement, although not significant (Cuccia et al., 2020). However, despite the MR imaging localization and dampening effects of the hydrogel, Fiducial markers are recommended and are currently the standard of care. They can help locate the prostate during treatment sessions and are used to match the original position determined by CT planning. A major disadvantage of OAR hydrogel is that the radiodensity of this hydrogel is similar to that of soft tissues such as the prostate and rectum. Consequently, these rectal spacers are difficult to visualize on CT scans, which can make it difficult to accurately contour the prostate and rectum. This can potentially lead to increased inadvertent radiation to surrounding structures during the planning phase if CT is the only modality available (Kamran et al., 2022). Due to intrafraction and interfractional movements of the prostate, the treatment plan may need to be altered between the planning phase and into treatment imaging based on changes in the patient’s anatomy with a 10-kV cone beam CT (CBCT) (Kamran et al., 2022). A newer product, iodinated contrast hydrogel with enhanced CT visibility, may improve the accuracy of prostate/rectum contouring during planning and visualization of the target region during treatment so that consistent therapy can be delivered. Previously, when PCa patients had contraindications to MRI, such as pacemakers, implantable cardioverter defibrillators, metallic foreign bodies, cochlear implants, or intracranial aneurysm clips, OAR was not an option.

The hydrogel is covalently bonded to iodine to prevent free-floating molecules in the body during degradation to prevent allergic reactions to iodine. The properties of the standard hydrogel (e.g., the transformation from liquid to solid components in fractions of a second, stability over 3 months during RT, and eventual clearance by the body) remain unchanged in the iodinated version (Space OAR, 2022). Thus, the hydrogel provides comparable dosimetric consistencies and relative prostate-to-rectum separation despite a smaller mean contoured volume. The non-iodinated hydrogel measures a significantly larger volume at 10.6 versus 8.9 mL when compared to the iodinated hydrogel on CT, likely due to excessive contouring due to the inability to accurately demarcate anatomical boundaries. This is hypothesized to be due to incorrect magnetic resonance imaging/computed tomography (MRI/CT) fusion techniques, which is exacerbated when the pre-procedural MRI and CT are performed on separate days (Kamran et al., 2022).

Clinical Data for Hydrogels in IMRT

Studies show that in patients who use a hydrogel rectal spacer, there is a significant decrease in radiation to the rectum. In addition, the Expanded Prostate Cancer Index Composite (a validated instrument that measures patient-reported health-related quality of life (QoL) after PCa treatment) has shown an improvement in bowel QoL in patients for whom a hydrogel rectal spacer was used (Kamran et al., 2022).
The use of a hydrogel rectal spacer also reduces the incidence of discomfort secondary to urinary frequency in the groups studied by 5%. In addition, the improvement in urinary QoL at the 3-year follow-up is statistically significant (Brenneman et al., 2021). The use of a hydrogel rectal spacer reduces radiation toxicity to the penile bulb and is associated with improved erectile function compared to groups where the hydrogel rectal spacer is not used (Brand et al., 2019). Rectal radiation reduction can be observed in patients regardless of prostate volume after hydrogel spacer placement. Absolute radiation reduction for prostates <40 mL and >80 mL can be reduced from 13% to 3% and from 12% to 2%, respectively. This benefit also occurs regardless of prostate-to-rectal distance, with a significant reduction in absolute rectal toxicity with the placement of a hydrogel rectal spacer. When the prostate-to-rectal space measures 0, an absolute reduction in rectal toxicity can be observed from 12.4% to 3.2% after hydrogel rectal spacer placement. This absolute reduction remains significant, decreasing from 12.2% to 2.0% when the prostate-to-rectal space is >2.2 mm before hydrogel rectal spacer placement (Brand et al., 2019).

Clinical Data for Hydrogels in SBRT

Lower and higher doses (hypofractionated) of SBRT improve cost and patient convenience relative to EBRT (Quinn et al., 2020). However, studies have demonstrated substantial genitourinary (GU) and GI toxicity in patients undergoing aggressive dose-escalated hypofractionated SBRT regimens (Kishan et al., 2019). Although these regimens achieved high rates of freedom from biochemical failure, increased rectal toxicity was observed. For example, a study of 91 patients who received an escalated dose of 45–50 Gy in 5 fractions demonstrated that all developed rectal ulcers on the anterior rectal wall, although they eventually resolved (Folkert et al., 2021, Zelefsky et al., 2020). Additionally, 5/91 patients developed a recto-urethral fistula requiring colostomy (Zelefsky et al., 2020). Studies have shown that when a hydrogel is used, patients undergoing dose-escalated SBRT regimens (37.5–45 Gy in 5 fractions) demonstrate a low risk of grade ≥2 late GI toxicity (Brand et al., 2019). Regardless of the total radiation dose delivered, rectal radiation exposure decreased by 29–56% across the measured dosimetric profile curve, represented as a percentage of the maximum prescribed radiation dose when rectal spacers are used

(Brand et al., 2019).

Studies of SBRT using 45 Gy in 5 fractions using a hydrogel have demonstrated a significant reduction in the incidence of rectal ulcers. A rectal ulcer rate of 14.3% can be observed by direct anoscopy in low-risk and intermediate-risk PCa. Furthermore, no subsequent grade ≥3 GI toxicity was observed with the hydrogel rectal spacer compared to patients without a spacer (Folkert et al., 2021, Zelefsky et al., 2020).

In SBRT with VMAT, dose coverage of the planned target volume is challenging when attempting to spare the rectum, bladder, and urethra. The use of hydrogels has been shown to improve target dose coverage and preservation of rectal radiation (Payne et al., 2021).

Previously, urethrogram-guided SBRT was used in patients with contraindications to MRI (Brand et al., 2019). Although a CT urethrogram aids in identifying the prostatic apex, there is greater uncertainty in the location of the anterior rectal wall relative to the prostate when using urethrogram-based treatment planning without MRI fusion assistance. This subset of patients has the potential to benefit from the use of iodinated hydrogel spacers to mitigate the risk of GI toxicity. Iodinated hydrogel is easily visualized on CT and helps delineate the remainder of the prostate-rectum interface for better-targeted SBRT.

Clinical Data for Hydrogels in BQT

BBTD is an accepted single-modality treatment for low-risk and favourable intermediate-risk PCa or as part of a combination regimen for unfavourable intermediate- and high-risk PCa (Conroy et al., 2020). BBTD produces higher biochemical progression-free survival rates when compared to EBRT and prostatectomy treatment regimens. Rectal toxicity after BBTD has been reported to be as high as 39% and is likely due to the proximity of the rectum to the implanted seeds in the prostate. Researchers have demonstrated successful placement of the hydrogel after seed implantation during the same procedure and have shown that placement of the hydrogel reduced the measured radiation dose to the rectum and demonstrated decreased acute rectal toxicity (Brand et al., 2019).

The hydrogel offers the additional clinical benefit of contouring and post-implant analysis, which is particularly advantageous in the setting of BBTD (Huang et al., 2020). Detailed contouring of the anterior rectal wall and posterior aspect of the prostate is essential for accurate dosimetry, which is most often calculated based on CT alone. A non-iodinated hydrogel, in the presence of oedema and bleeding around the prostate, may demonstrate adequate contouring and make accurate post-implant dosimetry challenging. Furthermore, streaking artifacts caused by BQT seeds may obscure the boundaries of the rectal wall. The iodinated cross-linked PEG component of OAR hydrogels improves visualization on CT images and is therefore beneficial in BBT.

Adverse Effects of Hydrogels

The hydrogel rectal spacer needle should be inserted under ultrasound guidance to maintain visibility of the needle tip and avoid penetration of the rectal wall (Huang et al., 2020). If the needle enters the rectal lumen at any time, the procedure should be abandoned to avoid infection and infiltration of the rectal wall. Some studies have shown that most cases in which the hydrogel was injected into the rectal wall resolve with conservative treatment and time. It is believed that the hydrogel is slowly resorbed over time. However, in some cases, surgical colostomy and surgical intervention are necessary (Brand et al., 2019). According to some studies, some important complications included severe anaphylaxis, recto-urethral fistula, abscess formation, and sepsis. Interventions such as abscess drainage, colostomy diversion, and intensive care unit (ICU) admission were required as additional management in some cases (Mc Laughlin et al., 2021). Further studies are needed to understand and gain knowledge about the potential rare and serious complications of this procedure.

Discussion

The results indicate that the hydrogel spacer is a safe and effective adjunct that may improve QOL outcomes for patients electing RT for PCa. Spacer placement was relatively straightforward for physicians experienced in transrectal or transperineal prostate procedures, with the vast majority of implants achieving significant rectal radiation dose reduction.

While significant rectal dose reduction is the expected outcome of prostate-rectum spacer placement, reduction to the penile bulb was not. The mechanism behind the penile bulb dose reduction is under investigation, but one theory suggests that the spacer-facilitated dose reduction to the rectum allows the dose-planning optimization algorithm to better reduce the dose to secondary structures such as the penile bulb. The significance is that the reduction in penile bulb dose may explain the unanticipated improvements in sexual QOL relative to the control group. Although the mechanism for the urinary QOL findings is still under investigation, radiation sparing of the erectile or vascular structures surrounding the bulb may be responsible for the sexual QOL findings. Higher doses of the bulb have been found to increase the risk of ED, adding credence to this theory (Roach et al., 2010). The ability to reduce dose to secondary structures when using prostate-rectum spacers is an area of ongoing investigation.

Although patients in the spacer arm demonstrated a lower rate of rectal pain adverse events in the acute phase (first 3 months), a significant reduction in overall rectal toxicity during the same period was not observed. One hypothesis is that any acute rectal toxicity benefit of the spacer may have been masked by toxicity secondary to unintended radiation of the small bowel or sigmoid colon. Recent evidence has suggested that patient-reported acute bowel toxicity is associated with doses between 20 and 40 Gy to these structures (Sini et al., 2017). These structures were not independently contoured in the radiation plans, as such further evaluation of potential differences (or lack thereof) between treatment arms is ongoing.

Although an acute rectal toxicity benefit was not measured, the significant long-term benefits (0% G2+ late rectal toxicity, improved rectal QOL) demonstrate that the spacer eliminated rectal injury during radiotherapy.

To better appreciate the low rate of toxicity related to SpaceOAR-treated patients, recently published IG-IMRT studies report G2+ late rectal toxicity rates ranging from 14% to 25% (Lee et al., 2016). In comparison, none (0%) of the 149 spacer patients in the SpaceOAR randomized controlled trial experienced G2+ late rectal toxicity at 37-month follow-up. This finding further suggests that PEG hydrogel spacer technology may significantly reduce long-term rectal toxicity, resulting in durable quality-of-life benefits.

The hydrogel spacer used in this study was found to be effective in improving patient-reported outcomes at 37 months. For example, the number of spacer patients needed to be treated to prevent 1 patient from experiencing significant improvement in disease (MID) declines in bowel quality of life at 37 months was 3.7. Similarly, the number of spacer patients needed to treat to prevent MID declines in urinary quality of life (7.7), erectile dysfunction (3.4), and MID declines in all 3 domains (bowel, urinary, and sexual) was 5.7. These results support the role of spacers in reducing rectal dose during prostate radiotherapy, leading to short- and long-term patient benefits (Wortel et al., 2016).

Although this is the first randomized trial, this hydrogel spacer has been evaluated in numerous other clinical trials. A multicenter pilot study evaluated the ability to safely apply the spacer, its ability to create and maintain space during IMRT, reduce radiation dose to the rectum, and its impact on toxicity for 12 months after radiotherapy (Uhl et al., 2013). In this study of 52 patients, the transperineal approach using a side-firing ultrasound probe mounted on a step stabilizer resulted in safe and effective spacer placement. Prostate-rectum spacer separation was ⩾7.5 mm in 95.8% of patients, resulting in a significant reduction of 8.0 Gy in the mean rectal dose. The gel was stable throughout RT, with imaging-confirmed uptake at 9–12 months. Through 12 months, the rate of grade 1 late GI toxicity was 4.3%, with no grade 2+ late GI toxicity in the study. Pinkawa et al followed 114 patients (54 spacers, 60 control) for a median of 63 months after prostate IMRT and published changes in 1.5- and 5-year quality of life data from baseline. Increases in mean QOL scores for bowel discomfort (>10 points from baseline) were reported more than 5 times more frequently by control patients at 1.5-year follow-up (32% vs 6%, P < .01), and patients treated with a hydrogel spacer had significantly fewer moderate to major problems with bowel urgency at 1.5 years (0% vs 13%, P < .01) and at 5 years (0 vs 14%, P = .01) relative to control patients. In line with the unexpected sexual QOL findings in the randomized clinical trial, the investigators also found that patients with a hydrogel spacer were significantly more likely to have erections sufficient for intercourse at 5 years post-treatment (24% vs. 3% P < .01) (Pinkawa et al., 2017). te Velde et al evaluated the impact of the hydrogel spacer on prostate IMRT dosimetry and toxicity in a study of 125 patients (65 spacers, 60 control) and found that rectal dosimetry parameters were all significantly lower in the spacer group, with an associated reduction in acute diarrhoea (13.8% vs. 31.7%, P = .02). In a study of 140 patients (30 spacers, 110 control) (Te Velde et al., 2017), Whalley et al found that the spacer significantly reduced radiation dose to the rectum and that at a median follow-up of 28 months, grade 1 late rectal toxicity was significantly less frequent in the hydrogel spacer group (16.6% vs 41.8%, P = 0.04) (Whalley et al., 2016).

Investigators have also compared hydrogel spacers with other potential spacing concepts. Wolf et al compared the hydrogel spacer with an absorbable saline-inflated balloon (Wolf et al., 2015). Both spacer products significantly reduced radiation dose to the rectum immediately after implantation, but the balloon exhibited >50% volume loss during EBRT, whereas the hydrogel volume remained fairly constant. This loss of balloon volume has recently been confirmed by other investigators, where a mean volume loss of 70.4% was observed at the end of radiotherapy. Chapet et al evaluated hyaluronic acid as a spacer in a phase 2 study of 36 patients (Chapet et al., 2015). Although the product appeared to be well tolerated and significantly reduced the radiation dose to the rectum, 1 patient developed a hematoma behind the bladder in the hours after spacer injection, requiring removal by laparotomy. Hyaluronic acid has also been shown to be degraded by therapeutic levels of radiation, and there have been reports of hypersensitivity reactions when used in other indications.

Conclusion

Physicians and patients newly diagnosed with PCa should become knowledgeable about the potential use of this technology when considering prostate RT. Furthermore, in addition to mitigating side effects and improving QOL, prostate-rectum spacers may potentially enable the development of radiation protocols investigating hypofractionation or other conventional dose escalation studies, especially in the setting of high-risk Pca. Na area not yet fully studied is whether spacers can offer safe delivery of RT in patients with inflammatory bowel disease, vascular disease, diabetes, or those requiring post-RT salvage with BQT or SBRT. Reducing the toxicity of salvage RT may allow patients with recurrent or residual localized cancer to undergo a salvage procedure. Further studies are needed to fully investigate these specific high-risk patient populations. Similar ydrogel used as neurosurgical sealants and abdominal adhesion barriers have been shown to prevent fibrosis after surgical procedures. Although it has not yet been demonstrated whether prostate-rectum hydrogel spacers prevent RT-induced prostate-rectum fibrosis, the potential for salvage prostatectomy after localized cancer recurrence could potentially be optimized.

PROSPERO Registration Number

1003612

Abbreviations

ASCENDE-RT - Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiotherapy, BATD - High-Dose Brachytherapy, BBTD - Low-Dose Brachytherapy, BQT - Brachytherapy, CaP - Prostate Cancer, CBCT - Cone Beam Computed Tomography kV, DE - Erectile Dysfunction, PD - Mean, EBRT - External Beam Radiotherapy, EPIC - Expanded Prostate Cancer Index Composite, GI - Gastrointestinal, GU - Genitourinary, Gy - Grays, IG-IMRT - Image-Guided Intensity Modulated Radiotherapy, IGRT - Image-Guided Radiotherapy, MID - Significant Improvement of Disease, PEG - Polyethylene Glycol, PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses, QOL- Health-Related Quality of Life Questionnaire, QV - Quality of Life, MRI - Nuclear Magnetic Resonance, MRI/CT - Magnetic Resonance/Computed Tomography, RT - Radiotherapy, SBRT - Stereotactic Radiotherapy, CT - Computed Tomography, ICU - Intensive Care Unit, VMAT - Volumetric Arc Radiotherapy.

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References

Arcangeli, G., Arcangeli, S., Pinzi, V., Benassi, M., Benassi, M., & Strigari, L. (2018). Optimal scheduling of hypofractionated radiotherapy for localized prostate cancer: A systematic review and metanalysis of randomized clinical trials. Cancer treatment reviews, 70, 22–29. https://doi.org/10.1016/j.ctrv.2018.07.003
Brand, D. H., Tree, A. C., Ostler, P., van der Voet, H., Loblaw, A., Chu, W., Ford, D., Tolan, S., Jain, S., Martin, A., Staffurth, J., Camilleri, P., Kancherla, K., Frew, J., Chan, A., Dayes, I. S., Henderson, D., Brown, S., Cruickshank, C., Burnett, S., … PACE Trial Investigators (2019). 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. The Lancet. Oncology, 20(11), 1531–1543. https://doi.org/10.1016/S1470-2045(19)30569-8
Brenneman RJ, Andruska N, Roy A, Waters MR, Fischer-Valuck BW, Schiff JP, Goddu SM, et al. Caracterização de um novo espaçador de hidrogel perirretal radiopaco para radioterapia de câncer de próstata. Internacional J. Radiat. Oncol. Biol. Física. 2021; 111 :e536.
Chapet, O., Decullier, E., Bin, S., Faix, A., Ruffion, A., Jalade, P., Fenoglietto, P., Udrescu, C., Enachescu, C., & Azria, D. (2015). Prostate hypofractionated radiation therapy with injection of hyaluronic acid: acute toxicities in a phase 2 study. International journal of radiation oncology, biology, physics, 91(4), 730–736. https://doi.org/10.1016/j.ijrobp.2014.11.027
Conroy, D., Becht, K., Forsthoefel, M., Pepin, A. N., Lei, S., Rashid, A., Collins, B. T., Lischalk, J. W., Suy, S., Aghdam, N., Hankins, R. A., & Collins, S. P. (2021). Utilization of Iodinated SpaceOAR Vue™ During Robotic Prostate Stereotactic Body Radiation Therapy (SBRT) to Identify the Rectal-Prostate Interface and Spare the Rectum: A Case Report. Frontiers in oncology, 10, 607698. https://doi.org/10.3389/fonc.2020.607698
Cuccia, F., Mazzola, R., Nicosia, L., Figlia, V., Giaj-Levra, N., Ricchetti, F., Rigo, M., Vitale, C., Mantoan, B., De Simone, A., Sicignano, G., Ruggieri, R., Cavalleri, S., & Alongi, F. (2020). Impact of hydrogel peri-rectal spacer insertion on prostate gland intra-fraction motion during 1.5 T MR-guided stereotactic body radiotherapy. Radiation oncology (London, England), 15(1), 178. https://doi.org/10.1186/s13014-020-01622-3
da Silva Barreto, G., Brito do Nascimento, J., Cristina Santos de Almeida, K., Carlos Marcolino Neto, J., & Lucas Ferreira Luz da Silva, S. (2024). The CRISPR therapy: A revolutionary breakthrough in genetic medicine. International Healthcare Review (online). https://doi.org/10.56226/88
Dobroski, A. U. B., Duarte, B. P. F., Tanganelli, C. B., Neto, E. M. O., Naddeo, M., Valdujo, N. S., Maluf, G., & Uyeda, M. (2025). Impact of Mutations in DNA Repair Genes in Lynch Syndrome: A Systematic Literature Review. International Healthcare Review (online). https://doi.org/10.56226/93
Folkert, M. R., Zelefsky, M. J., Hannan, R., Desai, N. B., Lotan, Y., Laine, A. M., Kim, D. W. N., Neufeld, S. H., Hornberger, B., Kollmeier, M. A., McBride, S., Ahn, C., Roehrborn, C., & Timmerman, R. D. (2021). A Multi-Institutional Phase 2 Trial of High-Dose SAbR for Prostate Cancer Using Rectal Spacer. International journal of radiation oncology, biology, physics, 111(1), 101–109. https://doi.org/10.1016/j.ijrobp.2021.03.025
Gay, H. A., & Michalski, J. M. (2018). Radiation Therapy for Prostate Cancer. Missouri medicine, 115(2), 146–150.
Huang, J., Liu, J., Fang, J., Zeng, Z., Wei, B., Chen, T., & Wei, H. (2020). Identification of the surgical indication line for the Denonvilliers' fascia and its anatomy in patients with rectal cancer. Cancer communications (London, England), 40(1), 25–31. https://doi.org/10.1002/cac2.12003
Instituto Nacional do Câncer. Consulta de dados médicos (PDQ). Prevenção do Câncer de Próstata. 2023. https://www.cancer.gov/types/prostate/hp/prostate-prevention-pdq
Kamran, S. C., McClatchy, D. M., 3rd, Pursley, J., Trofimov, A. V., Remillard, K., Saraf, A., Ghosh, A., Thabet, A., Sutphin, P., Miyamoto, D. T., & Efstathiou, J. A. (2022). Characterization of an Iodinated Rectal Spacer for Prostate Photon and Proton Radiation Therapy. Practical radiation oncology, 12(2), 135–144. https://doi.org/10.1016/j.prro.2021.09.009
Kenupp, M. G., Vianna, A., Uyeda, M., & Maluf, G. (2024). On Patients with Colorectal Cancer : Associations, prognosis, survival and effects of therapy performed in the intestinal microbiota. International Healthcare Review (online). https://doi.org/10.56226/83
Kishan, A. U., Dang, A., Katz, A. J., Mantz, C. A., Collins, S. P., Aghdam, N., Chu, F. I., Kaplan, I. D., Appelbaum, L., Fuller, D. B., Meier, R. M., Loblaw, D. A., Cheung, P., Pham, H. T., Shaverdian, N., Jiang, N., Yuan, Y., Bagshaw, H., Prionas, N., Buyyounouski, M. K., … King, C. R. (2019). Long-term Outcomes of Stereotactic Body Radiotherapy for Low-Risk and Intermediate-Risk Prostate Cancer. JAMA network open, 2(2), e188006. https://doi.org/10.1001/jamanetworkopen.2018.8006
Lee, W. R., Dignam, J. J., Amin, M. B., Bruner, D. W., Low, D., Swanson, G. P., Shah, A. B., D'Souza, D. P., Michalski, J. M., Dayes, I. S., Seaward, S. A., Hall, W. A., Nguyen, P. L., Pisansky, T. M., Faria, S. L., Chen, Y., Koontz, B. F., Paulus, R., & Sandler, H. M. (2016). Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 34(20), 2325–2332. https://doi.org/10.1200/JCO.2016.67.0448

Lloyd Williams, D. (2022). On Healthcare Research Priorities in the USA : From Long COVID to Precision Health, what else is new?. International Healthcare Review (online), 1(1). https://doi.org/10.56226/ihr.v1i1.14
Mandal, A., Clegg, J. R., Anselmo, A. C., & Mitragotri, S. (2020). Hydrogels in the clinic. Bioengineering & translational medicine, 5(2), e10158. https://doi.org/10.1002/btm2.10158
McLaughlin, M. F., Folkert, M. R., Timmerman, R. D., Hannan, R., Garant, A., Hudak, S. J., Costa, D. N., & Desai, N. B. (2021). Hydrogel Spacer Rectal Wall Infiltration Associated With Severe Rectal Injury and Related Complications After Dose Intensified Prostate Cancer Stereotactic Ablative Radiation Therapy. Advances in radiation oncology, 6(4), 100713. https://doi.org/10.1016/j.adro.2021.100713
Marques da Silva, M., Matias Cunha, C., Aquino, C., Aquino, L., & Fernanda Pizo Ferreira, P. (2025). SBRT for Uncomplicated Bone Metastases in the Spine from Lung Cancer: A literature Review. International Healthcare Review (online). https://doi.org/10.56226/92
Morris, W. J., Tyldesley, S., Rodda, S., Halperin, R., Pai, H., McKenzie, M., Duncan, G., Morton, G., Hamm, J., & Murray, N. (2017). Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate Cancer. International journal of radiation oncology, biology, physics, 98(2), 275–285. https://doi.org/10.1016/j.ijrobp.2016.11.026
Muralidhar, V., Mahal, B. A., Butler, S., Lamba, N., Yang, D. D., Leeman, J., D'Amico, A. V., Nguyen, P. L., Trinh, Q. D., Orio, P. F., 3rd, & King, M. T. (2019). Combined External Beam Radiation Therapy and Brachytherapy versus Radical Prostatectomy with Adjuvant Radiation Therapy for Gleason 9-10 Prostate Cancer. The Journal of urology, 202(5), 973–978. https://doi.org/10.1097/JU.0000000000000352
Payne, H. A., Pinkawa, M., Peedell, C., Bhattacharyya, S. K., Woodward, E., & Miller, L. E. (2021). SpaceOAR hydrogel spacer injection prior to stereotactic body radiation therapy for men with localized prostate cancer: A systematic review. Medicine, 100(49), e28111. https://doi.org/10.1097/MD.0000000000028111
Pinkawa, M., Berneking, V., Schlenter, M., Krenkel, B., & Eble, M. J. (2017). Quality of Life After Radiation Therapy for Prostate Cancer With a Hydrogel Spacer: 5-Year Results. International journal of radiation oncology, biology, physics, 99(2), 374–377. https://doi.org/10.1016/j.ijrobp.2017.05.035
Prada, P. J., Fernández, J., Martinez, A. A., de la Rúa, A., Gonzalez, J. M., Fernandez, J. M., & Juan, G. (2007). Transperineal injection of hyaluronic acid in anterior perirectal fat to decrease rectal toxicity from radiation delivered with intensity modulated brachytherapy or EBRT for prostate cancer patients. International journal of radiation oncology, biology, physics, 69(1), 95–102. https://doi.org/10.1016/j.ijrobp.2007.02.034
Quinn, T. J., Daignault-Newton, S., Bosch, W., Mariados, N., Sylvester, J., Shah, D., Gross, E., Hudes, R., Beyer, D., Kurtzman, S., Bogart, J., Hsi, R. A., Kos, M., Ellis, R., Logsdon, M., Zimberg, S., Forsythe, K., Zhang, H., Soffen, E., Francke, P., … Hamstra, D. A. (2020). Who Benefits From a Prostate Rectal Spacer? Secondary Analysis of a Phase III Trial. Practical radiation oncology, 10(3), 186–194. https://doi.org/10.1016/j.prro.2019.12.011
Roach, M., 3rd, Nam, J., Gagliardi, G., El Naqa, I., Deasy, J. O., & Marks, L. B. (2010). Radiation dose-volume effects and the penile bulb. International journal of radiation oncology, biology, physics, 76(3 Suppl), S130–S134. https://doi.org/10.1016/j.ijrobp.2009.04.094
Sini, C., Noris Chiorda, B., Gabriele, P., Sanguineti, G., Morlino, S., Badenchini, F., Cante, D., Carillo, V., Gaetano, M., Giandini, T., Landoni, V., Maggio, A., Perna, L., Petrucci, E., Sacco, V., Valdagni, R., Rancati, T., Fiorino, C., & Cozzarini, C. (2017). Patient-reported intestinal toxicity from whole pelvis intensity-modulated radiotherapy: First quantification of bowel dose-volume effects. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology, 124(2), 296–301. https://doi.org/10.1016/j.radonc.2017.07.005
Sistema SpaceOAR™ Vue. 2022. (acessado em 9 de dezembro de 2023). Disponível online: https://www.bostonscientific.com/content/dam/bostonscientific/spaceoar/vue/URO-855204-AA%20SpaceOAR%20VUE_Brief%20Summary.pdf
Song, C., & Xie, H. (2023). On Disparities in Breast Cancer Screening: An Analysis of Behavioral Risk Factor Surveillance Survey Data related to Racial/ Ethnic characteristics. International Healthcare Review (online). https://doi.org/10.56226/53
Te Velde, B. L., Westhuyzen, J., Awad, N., Wood, M., & Shakespeare, T. P. (2017). Can a peri-rectal hydrogel spaceOAR programme for prostate cancer intensity-modulated radiotherapy be successfully implemented in a regional setting?. Journal of medical imaging and radiation oncology, 61(4), 528–533. https://doi.org/10.1111/1754-9485.12580
Uhl, M., van Triest, B., Eble, M. J., Weber, D. C., Herfarth, K., & De Weese, T. L. (2013). Low rectal toxicity after dose escalated IMRT treatment of prostate cancer using an absorbable hydrogel for increasing and maintaining space between the rectum and prostate: results of a multi-institutional phase II trial. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology, 106(2), 215–219. https://doi.org/10.1016/j.radonc.2012.11.009
Whalley, D., Hruby, G., Alfieri, F., Kneebone, A., & Eade, T. (2016). SpaceOAR Hydrogel in Dose-escalated Prostate Cancer Radiotherapy: Rectal Dosimetry and Late Toxicity. Clinical oncology (Royal College of Radiologists (Great Britain)), 28(10), e148–e154. https://doi.org/10.1016/j.clon.2016.05.005
Wolf, F., Gaisberger, C., Ziegler, I., Krenn, E., Scherer, P., Hruby, S., Schätz, T., Forstner, R., Holzinger, J., Vaszi, A., Kametriser, G., Steininger, P., Deutschmann, H., & Sedlmayer, F. (2015). Comparison of two different rectal spacers in prostate cancer external beam

radiotherapy in terms of rectal sparing and volume consistency. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology, 116(2), 221–225. https://doi.org/10.1016/j.radonc.2015.07.027
Wortel, R. C., Incrocci, L., Pos, F. J., van der Heide, U. A., Lebesque, J. V., Aluwini, S., Witte, M. G., & Heemsbergen, W. D. (2016). Late Side Effects After Image Guided Intensity Modulated Radiation Therapy Compared to 3D-Conformal Radiation Therapy for Prostate Cancer: Results From 2 Prospective Cohorts. International journal of radiation oncology, biology, physics, 95(2), 680–689. https://doi.org/10.1016/j.ijrobp.2016.01.031
Zelefsky, M. J., Pinitpatcharalert, A., Kollmeier, M., Goldman, D. A., McBride, S., Gorovets, D., Zhang, Z., Varghese, M., Happersett, L., Tyagi, N., & Hunt, M. (2020). Early Tolerance and Tumor Control Outcomes with High-dose Ultrahypofractionated Radiation Therapy for Prostate Cancer. European urology oncology, 3(6), 748–755. https://doi.org/10.1016/j.euo.2019.09.006
Zijiu, C., Li, W., & Qin, J. (2025). Philosophical Reflections on Chinese Naturopathy against Malignant Tumours. International Healthcare Review (online). https://doi.org/10.56226/99