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A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Biodegradable Rectal Spacers for Prostate Cancer Radiotherapy

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and the biodegradable spacer insertion during radiotherapy for prostate cancer recommendation report group (SPACER RRG)

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Section 1: Recommendations and Key Evidence

OBJECTIVES

The objective of this guideline is to provide clinical practice recommendations for the use of biodegradable spacers for prostate cancer treatment.

TARGET POPULATION

Patients undergoing radiation treatment for localized prostate cancer.

INTENDED USERS

Radiation oncologists and genitourinary oncologists involved in the management of prostate cancer.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1
Biodegradable spacer insertion is a technology that may be used to decrease toxicity and maintain quality of life (QOL) in appropriately selected prostate cancer patients receiving radiotherapy (RT).
Qualifying Statements for Recommendation 1
• Spacer insertion should be performed by individuals trained in the use of transperineal interventional procedures and where there is institutional support. • Selection of appropriate patients remains to be fully defined but may include: those in whom standard rectal dose-volume criteria are not met; those treated with ultrahypofractionated RT; and those at higher baseline risk of rectal toxicity.
Key Evidence for Recommendation 1
• In a multicentre randomized controlled trial (RCT), 222 patients receiving the rectal spacer experienced significantly lower incidence and lower severity of long-term (greater than 3 months) rectal complications compared with patients not receiving spacers. There were significantly fewer patients experiencing grade 2 or greater long-term rectal toxicity (3 to 15 months) in the spacer (2%) group, compared with the non-spacer group (7%) ($p=0.044$). However, there were no significant differences observed in the rates of early rectal toxicity. Overall safety of the spacer was excellent, with no device-related adverse events, and no rectal infections or rectal complications [1]. • A follow-up report for this RCT involved 63% of the original sample at a median follow-up of 37 months. [2]. Grade ≥1 rectal toxicity at three years of follow-up was decreased by 75% in relative terms in the spacer group (hazard ratio [HR], 0.24; 95% confidence interval [CI], 0.06 to 0.97; $p<0.03$). No grade ≥2 rectal toxicity was observed in the spacer group (3-year rate: spacer 0%, non-spacer 6%, 95% CI, 2% to 17%; $p<0.015$) and one case of grade 3 rectal toxicity developed in the non-spacer group. A reduction was also seen in cumulative grade ≥1 urinary incontinence at three years ($p=0.046$), with no difference in other grade ≥1 urinary toxicities ($p>0.5$) or grade ≥2 urinary toxicity [2]. • There were no statistically significant differences in QOL measures for the one RCT examined in this report [1].

- In a cohort study of 167 patients, mean bowel function scores did not change for patients with a spacer in contrast to patients without a spacer more than one year after RT in comparison to baseline, with 0% versus 12% reporting a new moderate/big problem with passing stools ($p<0.01$) [3].
- The RCT discussed in this recommendation report received an overall judgment of "unclear' as to risk of bias, mainly due to uncertainty regarding missing data, the potential for selective reporting, and the study being funded by Augmenix Incorporated, makers of the biodegradable rectal spacer (SpaceOAR®) and two of the authors were stakeholders in the company.
- Evidence in the three non-randomized studies presented in Section 3 [3-5] showed small magnitude of benefit for relatively mild symptoms and were considered to be at "high risk of bias" mainly due to inadequate study design.

Interpretation of Evidence for Recommendation 1

The evidence is adequate to support the use of biodegradable rectal spacers for RT in patients with localized prostate cancer. However, given the low rates of toxicity observed overall in both arms of the RCT, there may be limited benefit to routine application of this technology. Further evidence to direct the appropriate selection of patients and to evaluate the efficacy of this technology beyond conventionally fractionated RT is warranted.

IMPLEMENTATION CONSIDERATIONS

Biodegradable rectal spacers are approved for use by Health Canada and thus implementation is left to the discretion of individual cancer centres. It is envisaged that each individual cancer centre may consider their local operational environment in facilitating the adoption of this technology. For example, centres with brachytherapy services may choose to adapt their system to allow for the transperineal insertion of the rectal spacer within the RT department, whereas those without brachytherapy services may choose to engage their local (interventional) radiology or urology departments. The associated costs, such as disposables, related to the transperineal procedure and the costs of the technology itself may need to be taken into account depending on the model of implementation.

FUTURE RESEARCH

More phase II/III randomized trials to further evaluate the efficacy of this technology are warranted. Additional research is also needed to identify the clinical and dosimetric risk factors that can determine those at greatest risk of rectal toxicity and who might benefit most from the use of this technology. As conventional fractionation was used exclusively in the completed RCT, evaluation of rectal spacer technology in the setting of hypofractionated RT is also warranted.

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Section 2: Recommendation Report Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 3.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

BACKGROUND FOR RECOMMENDATION REPORT

The PEBC was asked to develop recommendations for the use of biodegradable rectal spacer insertion for prostate cancer treatment. The PEBC identified an 'interventional procedural guidance (IPG)' document developed by the National Institute for health and Care Excellence (NICE) in the United Kingdom [6] and a Cochrane systematic review [7] assessing hydrogel spacers as a subsection of a document on interventions to reduce acute and late adverse gastrointestinal effects of pelvic RT as relevant to this report. A recent report on the use of hydrogel spacer insertion prepared for the Health Technology Assessment Unit of the McGill University Health Centre (MUHC) was also deemed relevant [8]. Since the above-mentioned documents differed in their conclusions as to the efficacy of biodegradable spacers, the relevant primary literature was assessed directly by the PEBC methodologist.

RECOMMENDATION REPORT DEVELOPERS

This recommendation report was developed by a Working Group consisting of four radiation oncologists (see Appendix 1) at the request of the biodegradable spacer insertion during radiotherapy for prostate cancer recommendation report group (hereby known as the SPACER RRG).

The Working Group was responsible for reviewing the evidence base, drafting the recommendations, and responding to comments received during the document review process. Conflict of interest declarations for all authors are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

RECOMMENDATION REPORT DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [9,10]. For Recommendation Reports this process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by a methodology experts, and final approval by the Sponsoring Committee.

The PEBC uses the AGREE II framework [11] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence-base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations were based on clinical evidence, along with consideration of implementation issues with magnetic resonance imaging. A list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation, using the ADAPTE framework [12], or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this project, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Standards, Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- Guideline developer websites: NICE, Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Health and Medical Research Council - Australia.

RECOMMENDATION REPORT REVIEW AND APPROVAL

Internal Review

The recommendation report was reviewed by the PEBC Report Approval Panel (RAP). The Working Group was responsible for ensuring the necessary changes were made. If those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again. Table 2-1 shows the Working Group's responses to the RAP review.

Table 2-1. Working Group Responses to RAP

RAP member	Working Group Response
The paper is a guideline on biodegradable hydrogel spacer as a rectal spacer for prostate cancer radiotherapy and I think the title should reflect this. The guideline really does not discuss or evaluate any other biodegradable spacers (i.e. hyaluronic acid, collagen saline-filled balloons, etc.)	While the majority of the evidentiary base concerned hydrogel spacers, we considered spacers of all types in our literature search and therefore have decided to leave the title unchanged. Of note, one trial that employed hyaluronic acid spacers (Prada et al.) was included and discussed in the report.
Well written – Magnitude of absolute benefit is small (2% vs. 7%) – Could highlight this	This has been pointed out in the recommendation section and in the discussion.

Report Approval by SPACER RRG

After internal review, the SPACER RRG reviewed the document on November 29th, 2018 and formally approved the document. Of the eight SPACER RRG members approached, one abstained and one did not submit a conflict of interest statement. All of the remaining six

eligible members approved (100%) the document. Table 2-2 shows comments addressed by the Working Group.

Table 2-2. Working Group Responses to Recommendation Report Group

SPACER RRG member	Working Group Response
I do have some concern that the main piece of evidence is a small phase 2 RCT that was sponsored by the company, conducted by some investigators with COIs and with short follow-up (< 60 mo). Margins used in the trial were hugely variable considering all patients got gold-seed IGRT (5 - 10mm CTV-PTV margin). There's no documentation of what the median (IQR) margins were in each group. I would have liked to see 4-5mm margins in both groups but alas that was the way the study was designed. Having said that, I think the conclusion is reasonably cautious given the above. It would be interesting to see a cost effectiveness analysis in the Canadian setting - SpaceOAR at $2700 (not including MD fees, disposibles or other personnel costs) doubles the cost of 60 Gy in 20fx and triples the cost of SBRT (40 Gy / 5fx).	Yes, we agree and the wording of the recommendation reflects that the evidence is only adequate to support the use of biodegradable rectal spacers for RT in patients with localized prostate cancer. We also state that since both arms of the RCT experienced low toxicity, there may be limited benefit to routine application of this technology.
Is there any data about when all hydrogel is either absorbed or congealed after instillation in humans/animals? Is it worthwhile to either allude to that data if available or to add a one liner indicating the absence of such data. One presumes this is going to be not at all like silicone implants.	We do not have evidence of rate of absorption but in addition to the estimates, in the RCT of 149 patients only 3 (2%) had any visible remnant of the get which consisted of water density cyst on MRI, as patients had MRI performed at 12 months after hydrogel insertion. This will be added to the findings sections of this report.

ACKNOWLEDGEMENTS

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- Sarah Deshpande for conducting a data audit.
- Sara Miller for copy editing.

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Section 3: Systematic Review

INTRODUCTION

External beam RT is a standard definitive treatment option for men with localized prostate cancer. Technical developments, including intensity modulation and image guidance, have allowed for greater precision in RT delivery to the prostate and enhanced sparing of surrounding normal tissues. However, optimal tumour control rates require escalated RT doses, and even with modern techniques, a portion of the anterior rectal wall remains exposed to considerable doses of radiation, which may result in acute and late toxicities. There is an unmet need for interventions that reduce rectal irradiation and thereby improve the therapeutic ratio of prostate RT.

The application of spacers placed between the prostate and rectum to create a 'space' is a logical solution to reduce the volume of rectal tissue receiving undesirable doses. A number of biodegradable materials have been evaluated for use as spacers, including polyethylene glycol hydrogels, hyaluronic acid, collagen, and saline-filled balloons. Early clinical studies with hydrogels have shown favourable outcomes. They are typically injected or inserted in a short procedure under transrectal ultrasound guidance using a transperineal approach. A distance of approximately 1.0 to 1.5 cm is usually achieved between the rectum and prostate, excluding the rectal wall from the high isodoses. Estimates suggest it takes approximately three months to liquefy by hydrolysis and absorb and clear the body via renal filtration [13]. A low incidence of major procedural adverse effects with hydrogel use has been reported. Hydrogel holds promise in establishing itself as an adjunct to standard of care in prostate RT and has been approved by Health Canada for this purpose.

This systematic review summarizes published reports on the effectiveness of the use of biodegradable spacers during RT for prostate cancer in reducing toxicity and maintaining QOL. The data provide the foundation for recommendations about the use of biodegradable rectal spacers during RT for prostate cancer patients in Ontario.

OBJECTIVES AND RESEARCH QUESTIONS

The Working Group developed the following objective for this guideline in consultation with the SPACER RRG:

- To assess the evidence regarding the use of biodegradable hydrogel spacers during RT for localized prostate cancer with particular reference to rectal toxicity and QOL following treatment.

From this objective, the following research question was derived to direct the search for available evidence to inform recommendations to meet the objectives.

- Does the use of biodegradable hydrogel spacers during RT for prostate cancer decrease rectal (and other) toxicities and maintain QOL following treatment?

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews and guidelines followed by a search for primary literature. These stages are described in subsequent sections.

Search for Existing Systematic Reviews and Guidelines

MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched for existing systematic reviews published since 2015. Relevant articles were identified by searches of MEDLINE (2015 – October 2018 week 40), EMBASE (2015 – 2018 week 40), and the Cochrane Library (2018). The reference lists of eligible articles were searched for relevant articles, and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) was searched for existing evidence-based practice guidelines. Expert colleagues were also asked to identify any relevant unpublished or published trials not otherwise identified. The complete MEDLINE and EMBASE search strategies are detailed in Appendix 2. This search identified three documents [6-8] (see Section 2 and subsequent sections for details)

Search for Primary Literature

Given that pre-2017 studies were identified in the NICE [6], Cochrane [7], and MUHC [8] documents, an updated search of the literature was conducted from June 2017 to June 2018 to supplement the existing primary literature. The subject was searched using MEDLINE (2017 through October, 2018), EMBASE (2017 through October, 2018), the Cochrane Central Register of Controlled Trials (OVID CCTR: August 2018), and the Database of Abstracts of Reviews of Effects (OVID DARE: 1st quarter 2018). In addition, the proceedings of the meetings of the ASCO (2017 to 2018), the American Society of Therapeutic Radiology and Oncology (ASTRO; 2017 to 2018), the Canadian Association of Radiation Oncology (CARO; 2009 to 2018) and the European Society for RT and Oncology (ESTRO; 2017 to 2018) were searched for relevant abstracts. Reference lists of studies deemed eligible for inclusion were scanned for additional citations. The literature search of the electronic databases combined disease-specific terms (prostate cancer, prostate carcinoma, etc.) and treatment-specific terms (RT, biodegradable spacers, etc.) (Appendix 2).

Study Selection Criteria and Process

Articles were eligible for inclusion in the systematic review if they met the following criteria:

- They were randomized controlled trials (RCTs).
- They were cohort (comparative) studies with contemporaneous controls.
- They compared patients receiving biodegradable hydrogel spacers to those not receiving spacers.
- They assessed adults aged ≥18 years with localized prostate cancer undergoing RT as part of cancer treatment.
- They reported on acute and/or late toxicities.

Studies were excluded if they:

- Were case reports, case series, case studies, commentaries or editorials.
- Had a sample size of fewer than 30 per group (non-RCTs only).
- Reported only on the technical aspects of biodegradable spacers.
- Reported only on dosimetric surrogates as outcomes.
- Were non-English-language articles (translation issues).

Data Extraction and Assessment of Study Quality and Potential for Bias

All relevant papers identified by the primary literature search were assessed against the above selection criteria independently by one of the authors (JB) (see Appendix 1 for a list of authors of this report). Uncertainties regarding eligibility were subsequently resolved by consensus of all the authors. The methodological quality of eligible studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [14] and "ROBINS-I"[15], a tool for assessing the risk of bias in non-randomized studies of interventions [16]. Data extraction was performed by one of the authors (JB), while a second reviewer (PC or SM or WK or DD) acted as an independent auditor to verify the accuracy of the data extraction.

Synthesizing the Evidence

A quantitative analysis of the trial data was planned for the outcomes of interest if the authors deemed it appropriate (i.e., clinical homogeneity of the treatment regimens and patient populations). When data were available from two or more trials, a meta-analysis would be performed using Review Manager (RevMan 5.3.1) [16] provided by the Cochrane Collaboration. The HR is the preferred statistic for pooling time-to-event outcomes because it incorporates data from the entire Kaplan-Meier curve and allows for censoring. When available, the HR would be extracted directly from the most recently reported trial results. The variances of the HR estimates would be calculated from the reported confidence CIs or p-values using the methods described by Parmar et al. [17]. Qualitative assessment of the data, along with consideration of implementation issues with MR, also informed the recommendations.

RESULTS

Overview of Existing Systematic Reviews and Guidelines

As previously indicated, the following three relevant documents were identified: 1) a NICE IPG document [6], 2) a Cochrane review [7], and 3) an MUHC technology assessment report [8].

The NICE document searched databases for studies relevant to biodegradable spacer insertions to reduce rectal toxicity, covering the period up to April 2017. The report included 1074 patients from one RCT [1], one quasi-RCT [4], two cohort studies [18,19], and other non-comparative studies. The report concluded that "current evidence on the safety and efficacy of insertion of a biodegradable spacer to reduce rectal toxicity during RT for prostate cancer is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit" [6].

The Cochrane review was much broader in scope than the NICE document, examining a variety of prophylactic interventions to reduce adverse gastrointestinal effects among adults receiving radiotherapy to treat primary pelvic cancers (literature searched up to November 2017). For the spacer insertions component of the review, one RCT [1] and one quasi-RCT [4] reporting on approximately 300 patients were included. The review concluded that low-certainty evidence on balloon and hydrogel spacers suggest that these interventions for prostate cancer RT may make little or no difference to genitourinary (GI) outcomes" [7].

The MUHC technology assessment report examined the efficacy, safety, and cost-effectiveness of biodegradable spacers, and undertook a budget impact analysis to assess suitability for adoption into MUHC practice. They identified one RCT [1] and five comparative non-RCTs [3,5,20-22] examining over 800 patients. They found that the hydrogel spacer was effective in reducing the amount of radiation to the rectum; however, they concluded that it was unclear whether the reductions translate into lower rectal toxicity and improved QOL.

They concluded that "given the limited and inconclusive evidence of the clinical benefit of SpaceOAR®, and the high costs associated with its use at the MUHC routine use of SpaceOAR® in prostate cancer patients receiving RT is not approved" [8].

Since these documents differed in their conclusions as to the efficacy of biodegradable spacers, the relevant primary literature from the existing reviews was extracted and assessed directly by the PEBC methodologist. Studies that met our inclusion criteria were one RCT [1], one quasi-RCT [4], and two of the cohort studies identified above [3,5]. The Prada et al. [4] study identified as a quasi-RCT by NICE and Cochrane will be referred to as a cohort/non-RCT study in the remainder of this report, since it could not be determined if any (or what type of) quasi-randomization assignment occurred (e.g., randomized by birthdate, medical record number, time of recruitment, etc.). The remaining comparative studies listed above were excluded from this report either because they did not include an outcome of interest [19,21], the sample size in one of the groups was less than 30 [18], or because there was no comparison group of interest to the current review [22].

Literature Search for Post-2017 Studies

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram summarizing this information is provided in Appendix 3.

One hundred three articles were identified and retrieved from the MEDLINE (n=81) and EMBASE (n=22) databases, and no additional records were identified through other sources. After duplicates were removed from the combined search results, 92 articles were assessed by title and abstract for possible inclusion in the evidence summary. Of these, 60 articles were rejected at the title level and the remaining 32 were assessed at the level of full text.

No new studies were identified in the updated search. Updates of four studies [1,3-5] identified previously in the reports identified above [6-8] were included in this recommendation report. The most recent publication was used where duplicate reports of the same outcomes existed.

Study Design and Quality

One RCT (with two publications) [1,2] and three cohort studies [3-5] were identified in this review.

Appendix 4 contains the quality assessment for the four studies assessed in this review. In the RCT by Mariados et al. [1], it was "unclear" how patient sequence generation was generated and whether group allocation was concealed. Although attrition was low in the trial, only 63% of participants were included in the three-year follow-up and, thus, it was "unclear" whether incomplete data were appropriately addressed in the study [2]. As well, only percentages (and not absolute numbers) were given for some of the final results and thus it was "unclear" exactly how many individuals were in each group and whether selective reporting was a potential bias in the study. Finally, this RCT was funded by Augmenix Incorporated, makers of the SpaceOAR®, and two of the authors were shareholders; thus, it was "unclear" if these factors potentially created other unknown bias in the study. The study was rated as "low" on risk of bias for blinding of participants and outcome assessors. The study received an overall judgement of "unclear" as to risk of bias (see Appendix 4).

The three cohort studies were judged as "high risk of bias" for confounding, given their non-randomized nature. The study by Pinkawa et al. [3] was judged at "low" risk of bias for selection of participants into the study, classification of interventions, and departure from intended intervention since participants were consecutive and incident cases, and were prospectively recruited. It was "unclear" as to whether there was any bias introduced in the study due to the possibility of missing data and in selection of the reported results. Finally, potential bias in measurement of outcomes was considered "moderate" since some patient

data were collected retrospectively. The study received an overall judgement of "high risk of bias" (see Appendix 4).

In the study by Prada et al. [4] it was "unclear" whether patents were selected consecutively and whether there was bias due to missing data. The study was judged to be at a "low" risk for bias on classification of intervention and bias due to departures from intended interventions. Risk of bias due to measurement of outcomes, and in selection of the reported results was considered high. The study received an overall judgement of "high risk of bias" (see Appendix 4).

In the study by Te Velde et al. [5] it was "unclear" whether patents were selected consecutively and whether there was bias due to missing data or in selection of the reported results. The study was judged to be at a "moderate" risk for bias on classification of intervention and in measurement of outcomes, due to its retrospective nature. Risk of bias due to classification in departure from intended interventions was considered low. The study received an overall judgement of "high risk of bias" (see Appendix 4).

Study Characteristics

Table 3-1 shows the characteristics of the four studies selected for inclusion. Mariados et al. [1] randomized 222 men with low-risk or intermediate-risk prostate cancer 2:1 to spacer hydrogel (n=149) or control (n=73). The study was performed at 20 centres in the United States between 2012 and 2016 and the men were blinded to randomization. Fiducial markers were placed for image guidance during spacer placement and anesthesia was administered per investigator discretion. The men received computed tomography and magnetic resonance imaging planning scans following the procedure and underwent image-guided intensity-modulated RT (79.2 Gy in 44 fractions). Spacer safety and impact on rectal irradiation, toxicity, and QOL were assessed up to 15 months [1].

Prada et al. [4] examined 69 consecutive outpatients enrolled in a clinical trial with low- and intermediate-risk prostate cancer between January 2005 and July 2006. One group received brachytherapy with permanent seed implant of I-125 along with a hyaluronic acid spacer to protect the rectal wall; the control group received brachytherapy with permanent implant of I-125 alone. Six to eight cubic centimetres of hyaluronic acid was injected into the perirectal fat, to increase the distance between the prostate and the anterior rectal wall. The median follow-up was 18 months [4].

Pinkawa et al. [3] examined a group of 167 consecutive patients receiving treatment of the prostate plus/minus base of the seminal vesicles without pelvic lymph nodes with RT with 2 Gy fractions up to 76 Gy (without hydrogel, n=66) or 76 to 80 Gy (with hydrogel, n=101) treated in a single institution between 2010 and 2013. The injection of 10 mL hydrogel was performed under transrectal ultrasound guidance after dissecting the space between prostate and rectum with a saline/lidocaine solution under local anesthesia. Patients were interviewed prospectively before RT, at the last day of RT, and at a median of two and 17 months after RT. The numbers of recorded bowel problems during the first two years after RT were compared [3].

Te Velde et al. [5] retrospectively compared 125 patients with localized prostate cancer between 2014 and 2015; 65 patients received hydrogel spacers (inserted by five different urologists) and 60 patients, treated over the same time period, did not receive the hydrogel spacers. Patients were treated with 81 Gy in 45 fractions of intensity-modulated RT over nine weeks. Planning aims included restricting rectal doses to V40 Gy <35%, V65 Gy <17%, and V75 Gy <10%. Gel volumes for the spacers were at the urologist's discretion and generally measured between 5 and 8 mL. Acute toxicity assessments covered radiation-induced rectal toxicity including diarrhea, proctitis, fecal incontinence, and hemorrhoids and were evaluated weekly during RT and at 12 weeks [5].

Table 3-1. Study Characteristics

Study	Population	Radiation treatment received	Treatment groups	Follow-up/ predictors and outcomes
Mariados, 2015 [1], Hamstra, 2017 [2] Single-blinded RCT, US multicentre	Men with clinical stage T1 or T2 PC recruited between 2012-13 (N=222 – 63% data reported in Hamstra, 2017); Mean age: spacer group 66.4 yrs.; control: 67.7 yrs.	IG-IMRT 79.2 Gy in 1.8-Gy fractions	Spacer Group (n=149): Transperineal injection of absorbable hydrogel spacer (and fiducial marker placement)) Control (n=73): No transperineal injection (fiducial marker placement only)	15 mos. Mariados, 3 yrs. Hamstra/ GI toxicity: Acute and late (CTCAE v4) QOL
Prada, 2009 [4] Prospective Cohort	Men with low- and intermediate-risk PC tumours (n=69); Med. Age spacer group 68 yrs., control 69 yrs.	BT with implanted I-125 seeds; prescription dose of 145 Gy to the isodose	Spacer Group (n=36): Transperineal injection of 6 - 8 ml of hyaluronic acid in the perirectal fat after the implantation of I-125 seeds Control (n=33): no transperineal hyaluronic acid injection	Med. 26 Mos./ GI toxicity: RTOG Rectal bleeding (CTCAE v2)
Pinkawa, 2017 [3] Prospective Cohort	167 consecutive (prospective) men who received prostate RT during the yrs. 2010 to 2013; Med. Age spacer group 72 yrs., Control 73 yrs.	RT with 2 Gy fractions up to 76 Gy (without hydrogel, n = 66) or 76-80 Gy (with hydrogel, n = 101)	Spacer Group (n=101): Injection of 10 mL hydrogel performed under TRUS guidance after dissecting the space between prostate and rectum with a saline/lidocaine solution. Control Group (n=66): non-spacer injection	17 mos. / bowel symptoms
Te Velde, 2017 [5] Retrospective Cohort	Retrospective analysis of patients with localised prostate cancer (n=125); Med. age spacer group 71.5 yrs., control 72.3 yrs.	81 Gy prostate IMRT	Spacer Group (n=65): spacer inserted by a transperineal approach by the referring urologists who had BT training and experience. Control Group (n=60) non-spacer	3 mos. / rectal toxicities

BT = Brachytherapy; CTCAE = Common Terminology Criteria for Adverse Events; HDR = high dose rate; IG = image guided; IMRT = intensity-modulated radiotherapy; PC = prostate cancer; QOL = quality of life; RCT = randomized controlled trial; RT = radiotherapy; RTOG = radiation therapy oncology group; TRUS = transrectal ultrasound

Outcomes

Mariados et al. [1] published 15 month findings regarding use of the hydrogel spacer. Patients receiving the rectal spacer experienced significantly lower incidence and severity of long-term (greater than 3 months) rectal complications compared with patients not receiving spacers. There were significantly fewer patients experiencing an absence of grade 2 or greater long-term rectal toxicity (3 to 15 months) with a 2.0% and 7.0% late rectal toxicity in the spacer and the non-spacer groups (p=0.044), respectively. However, there was no significant difference observed in the rates of early rectal toxicity. Overall safety of the spacer was excellent, with no device-related adverse events (AE), no rectal infections, rectal complications, or other AEs [1].

A follow-up involving 63% of the original sample [2] found grade ≥1 rectal toxicity at three years of follow-up was decreased by 75% in the spacer group (spacer: 2%, 95% CI, 1% to 6%; non-spacer: 9%, 95% CI, 4% to 20%; HR 0.24, 95% CI, 0.06 to 0.97; p<0.03). No grade ≥2 rectal toxicity was observed in the spacer group (3-year rate: spacer 0%, non-spacer 6%, 95% CI, 2% to 17%; p<0.015) and one case of grade 3 rectal toxicity developed in the non-spacer group. A reduction was also seen in cumulative grade ≥1 urinary incontinence at three years (spacer: 4%, 95% CI, 2% to 10%; non-spacer: 15%, 95% CI, 8% to 29%; p=0.046), with no difference in other grade ≥1 urinary toxicities (p>0.5) or grade ≥2 urinary toxicity. Of 149 patients, only 3 (2%) had any visible remnant of the gel, which consisted of water density cyst on MRI, as patients had MRI performed at 12 months after hydrogel insertion [2].

The Mariados et al. [1] study showed a moderate decline in QOL (assessed according to the function and bother score of the Expanded Prostate Cancer Index Composite [EPIC]) with 12% and 21% of spacer and control patients, respectively, experiencing 10-point declines at 15 months (p=0.09). At 36 months, 5% of men in the spacer group had a non-significant decline in bowel QOL compared with 21% in the non-spacer group (p=0.09) [2].

In the Prada study, the spacer and non-spacers groups were similar in tumour, treatment, and dosimetric characteristics. The spacer group had a significantly smaller incidence of mucosal damage at the proctoscopic examinations (5% vs. 36%, p=0.002) and no macroscopic rectal bleeding (0% vs. 12%, p=0.047) compared with the non-spacer group. No toxicity outcomes were seen from the hyaluronic acid or its injection [4].

In the Pinkawa study, baseline patient characteristics were well balanced. The spacer group needed less treatment for bowel symptoms (0 vs. 11%; p<0.01) and endoscopic examinations (3 vs. 19%; p<0.01) were performed less frequently compared with the non-spacer group. In QOL change measures after RT, in comparison to baseline, mean bowel function scores did not change for patients with a spacer in contrast to patients without a spacer (mean decrease of 5 points) >1 year after RT in comparison to baseline, with 0 vs. 12% reporting a new moderate/big problem with passing stools (p<0.01). No other QOL measures (urinary, sexual, hormonal), relative to baseline, were significant. Statistically significant improved differences for the spacer group were found for the self-reported symptoms of "loose stools" (p=0.003) "bloody stools" (p<0.001), "painful bowel movements" (p<0.001), and "frequency of bowel movements" (p=0.004) compared with the non-spacer group [3].

In the study by Te Velde et al., rectal volume parameters were all significantly lower in the spacer group, with an associated reduction in acute diarrhea (13.8% vs. 31.7%). There were no significant differences in the very low rates of acute and late fecal incontinence or proctitis [5]. Toxicity outcomes are reported in Table 3-2.

Table 3-2. Toxicity Outcomes

Study	Rectal/Bowel	Urinary	Other/Overall
Mariados, 2015 [1], Hamstra, 2017 [2] Single-blinded RCT, US multicentre **With spacer vs. without spacer**	Rates of grade ≤1 rectal or procedural adverse events at first 6 months 34.2% vs. 31.5%, p=0.7 Acute rectal pain 2.7% vs. 11.1%, **p=0.022** Acute (<3 mos.) – rectal toxicity Grade0 73% (108/148) vs. 68% (49/72); Grade1 23% (34/148) vs. 27.8% (20/72); Grade>2 4.1% (6/148) vs. 4.2% (3/72); p=0.525 Late (3 to 15 mos.) – rectal toxicity Grade0 98% (145/148) vs. 93% (66/71); Grade1 2% (3/148) vs. 5.6% (4/71); Grade>2 0% (0/148) vs. 1.4% 1/71); **p=0.044** Score Late (15 mos. To 3 yrs.) – rectal toxicity (Hamstra) Grade 1+ 2.0 (95% CI 4-20%) vs. 9.0 (95% CI 1-6%), HR 0.24 (95% CI 0.06-0.97) **p<0.03**; Grade>2 0% vs. 5.7%, **p<0.015** Mean change QOL bowel function (3mos.) 5-pt. 49% vs. 47%, NS; 10-pt. 32% vs. 31%, NS Mean change QOL bowel function (6mos.) 5-pt. 24% vs. 32%, NR; 10-pt. 12% vs. 19%, NR Mean change QOL bowel function (12mos.) 5-pt. 24% vs. 32%, NR; 10-pt. 15% vs. 20%, NR Mean change QOL bowel function (15mos.) 5-pt. 25% vs. 34%, NR; 10-pt. 12% vs. 21%, **p=0.009** Mean change QOL bowel function (36mos.) 5-pt. 41% vs. 41%, **p=0.009**; 10-pt. 5% vs. 21%, p=0.14	Acute (<3 mos.) – Urinary toxicity Grade0 9.5% (14/148) vs. 9.7% (7/72); Grade1 52.7% (78/148) vs. 45.8% (33/72); Grade>2 37.8% (56/148) vs. 44.4% (32/72); p=0.488 Late (3 to 15 mos.) – Urinary toxicity Grade0 90.5% (134/148) vs. 91.5% (65/71); Grade1 2.7% (4/148) vs. 4.2% (3/71); Grade>2 6.8% (10/148) vs. 4.2% (3/71); p=0.622 Score Late (15 mos. To 3 yrs.) - Urinary toxicity (Hamstra) Grade 1+ 4 (95% CI 2-10%) vs. 15 (95% CI 8-29%), HR 0.36 (95% CI 0.12 -1.1) p=0.046; Grade>2 7% vs. 7%, p=0.7	Overall adverse events 96.6% vs. 100%, p=NS Serious adverse events 13.4% vs. 15.1%, p=NS
Prada, 2009 [4] Pseudo-RCT, US multicenter **Hyaluronic acid vs non-hyaluronic acid**	No toxicity in fat or in rectal function. Mucosal damage post therapy 5% (2/36) vs. 36% (12/33), p=0.002 Macroscopic rectal bleeding 0 vs. 12% (4/23), p=0.047 No side effects related to injection or hyaluronic acid		
Pinkawa, 2017 [3] Prospective study -	QOL changes after RT in comparison to baseline mean (quartiles)[a] – Bowel function End of RT 11 (3;9;18) vs. 14 (0;11;21) 2	QOL changes after RT in comparison to baseline mean (quartiles)[a] - Urinary function End of RT 10 (0;7;17) vs. 13 (0;10;20)	QOL changes after RT in comparison to baseline mean (quartiles)[a] - Sexual function

Table 3-2. Toxicity Outcomes

Study	Rectal/Bowel	Urinary	Other/Overall
Germany **With spacers vs. without**	mos. after RT 4 (0;4;11) vs. 5 (-4;0;7) >1 yr. after RT *0 (-4;0;4)* vs. *5 (0;4;11)*, p<0.01 <u>Rectal urgency ≥ once a day</u> Before RT 16% vs. 11%, p=NS End of RT 36% vs. 44%, p=NS 2 mos. RT 24% vs. 18%, p=NS >1 yr. after RT 12% vs. 11%, p=NS <u>Uncontrolled leakage of stool ≥ once a day</u> Before RT 7% vs. 7%, p=NS End of RT 14% vs. 16%, p=NS 2 mos. RT 11% vs. 17%, p=NS >1 yr. after RT 7% vs. 8%, p=NS <u>Loose or liquid stools ≥ rarely</u> Before RT 47% vs. 41%, p=NS End of RT 64% vs. 73%, p=NS 2 mos. RT 58% vs.56 %, p=NS >1 yr. after RT 45% vs. 63%, p=0.003 <u>Bloody stools ≥ rarely</u> Before RT 7% vs. 4%, p=NS End of RT 14% vs. 20%, p=NS 2 mos. RT 10% vs. 24%, p=NS >1 yr. after RT 22% vs. 10%, p=0.01 <u>Painful bowel movement ≥ rarely</u> Before RT 14% vs. 23%, p=NS End of RT 47% vs. 50%, p=NS 2 mos. RT 24% vs. 23%, p=NS >1 yr. after RT 10% vs. 27%, p<0.01 <u>>2 days bowel movement</u> Before RT 18% vs. 7%, p=NS End of RT 28% vs. 31%, p=NS 2 mos. RT 17% vs. 26%, p=NS >1 yr. after RT 6% vs. 16%, p=0.04 <u>Crampy pain (abdomen/rectum ≥ once day</u> Before RT 2% vs. 0%, p=NS End of RT 3% vs. 7%, p=NS 2 mos. RT 2% vs. 3%, p=NS >1 yr. after RT 1% vs. 0%, p=NS	2 mos. after RT 2 (0;0;5) vs. 4 (0;0;7) >1 yr. after RT -1 (0;0;0) vs. -1 (0;0;0)	End of RT 12 (0;8;22) vs. 10 (0;6;16) 2 mos. after RT 6 (0;5;12) vs. 8 (-1;5;15) >1 yr. after RT 6 (-3;5;18) vs. 6 (-1;8;18) <u>QOL changes after RT in comparison to baseline mean (quartiles)[a] - Hormonal function</u> End of RT 5 (0;0;10) vs. 7 (0;0;15) 2 mos. after RT 3 (-5;0;10) vs. 4 (0;0;13) >1 yr. after RT -2 (-10;0;5) vs. -2 (-10;0;5)
Te Velde, 2017 [5]	<u>During RT - diarrhea</u> Grade1 86.2% vs. 68.3%, p=0.02 Grade2 13.8% vs. 31.7%, p=0.02		

Table 3-2. Toxicity Outcomes

Study	Rectal/Bowel	Urinary	Other/Overall
Retrospective study Australia **SpaceOAR vs. non-SpacOAR**	Grade3 0% vs. 0%, p=1 12 wks. after RT - diarrhea Grade1 95.4% vs. 95.0%, p=1 Grade2 4.6% vs. 5.0%, p=1 Grade3 0% vs. 0%, p=1 During RT – fecal incontinence Grade1 96.9% vs. 96.7%, p=1 Grade2 3.1% vs. 3.3%, p=1 Grade3 0% vs. 0%, p=1 12 wks. after RT – fecal incontinence Grade1 100% vs. 98.3%, p=0.5 Grade2 0% vs. 1.7%, p=0.5 Grade3 0% vs. 0%, p=1 During RT – proctitis Grade1 86.2% vs. 85.0%, p=1 Grade2 9.2% vs. 13.3%, p=0.6 Grade3 4.6% vs. 1.7%, p=0.6 12 wks. after RT – proctitis Grade1 98.5% vs. 95.0%, p=0.3 Grade2 1.5% vs. 5.0%, p=0.3 Grade3 0% vs. 0%, p=1 During RT – hemorrhoids Grade1 72.3% vs. 76.7%, p=0.7 Grade2 23.1% vs. 20.0%, p=0.8 Grade3 4.6% vs. 3.3%, p=1 12 wks. after RT – hemorrhoids Grade1 96.9% vs. 88.3%, p=0.09 Grade2 3.1% vs. 11.7%, p=0.09 Grade3 0% vs. 0%, p=1		

[a] (positive change corresponds to decreasing—worse—quality of life scores). CI = confidence interval; HR = hazard ratio; NR = not reported; NS = not significant; QOL = quality of life; RT = radiotherapy

Ongoing, Unpublished, or Incomplete Studies

There were no ongoing, unpublished or incomplete studies identified for this report.

DISCUSSION

There was one RCT [1,2] and three non-RCTs [3-5] identified in this review. We concluded that biodegradable spacer insertion during RT is a technology that may be used to decrease toxicity and maintain QOL in appropriate patients with prostate cancer. Selection of appropriate patients remains to be fully defined but may include those in whom standard rectal dose-volume criteria are not met; those treated with ultrahypofractionated RT; and those at higher baseline risk of rectal toxicity. It should be noted that spacer insertion should be performed by individuals trained in the use of transperineal interventional procedures.

Although there was only one RCT examining a biodegradable rectal spacer, it was concluded this was adequate evidence to support its use, provided institutional procedures are in place. In the multicentred RCT patients experienced significantly lower incidence and severity of long-term (greater than 3 months) rectal complications compared with patients not receiving spacers and there were significantly fewer patients experiencing an absence of grade 2 or greater long-term rectal toxicity (3 to 15 months) [1]. A follow-up to this RCT involving 63% of the original sample found grade ≥1 rectal toxicity at three years of follow-up decreased by 75% and no grade ≥2 rectal toxicity in the spacer group. A significant reduction was also seen in cumulative grade ≥1 urinary incontinence at three years in the spacer group compared with the non-spacer group [2]. However, the overall rates of late rectal toxicity in both arms of the RCT were low and absolute rates of grade ≥2 were 0% (no-spacer) versus 5.7% (spacer).

There is lack of data as to the most appropriate patients that would be likely to benefit from the use of such technology as the magnitude of benefit in this population is likely to be modest if it were routinely applied. This technology has not been tested in RCTs beyond conventional fractionation and should be the subject of further studies as well as examination of factors that may help to select those individuals that are at higher risk of toxicity. Until such data are available, in our expert opinion, it may be prudent to use this technology in selected patients that might include the following: those in whom standard rectal dose-volume criteria are not met; those treated with ultrahypofractionated RT; and those at higher baseline risk of rectal toxicity.

Our findings are consistent with that of the NICE document, which states that "current evidence on the safety and efficacy of insertion of a biodegradable spacer to reduce rectal toxicity during RT for prostate cancer is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit" [6]. In contrast, the Cochrane review concluded that "low-certainty evidence on balloon and hydrogel spacers suggest that these interventions for prostate cancer RT may make little or no difference to GI outcomes" [7]. However, in contrast to the NICE document and the current review, the Cochrane review had a much broader remit and examined a large number of differing technologies, concentrating mainly on different RT techniques and doses in patients undergoing RT for pelvic malignancies.

The MUHC technology assessment concluded that "given the limited and inconclusive evidence of the clinical benefit of SpaceOAR®, and the high costs associated with its use at the MUHC routine use of SpaceOAR® in prostate cancer patients receiving RT is not approved" [8]. The MUHC report was examining their specific situation based on their cost/funding institution's model and made the assumption that the only reduction in toxicity that was of concern was grade 2 or more rectal toxicity. Furthermore the report used data from the preliminary RCT publication and rates of grade ≥2 toxicity increased particularly in the non-spacer patients with further follow-up, as was reported in the final results of the RCT. The

MUHC document reported on the associated costs for their institution in Quebec. Economic analyses fall outside the mandate and expertise of the PEBC, and are out of scope for this document.

CONCLUSIONS

Biodegradable spacer is a technology that may be used to decrease toxicity and maintain QOL in appropriately selected patients with prostate cancer who are receiving RT. As conventional fractionation was used exclusively in the completed RCT, evaluation of rectal spacer technology in the setting of hypofractionated RT is also warranted. Additional research is also needed to identify the clinical and dosimetric risk factors that may determine those at greatest risk of rectal toxicity and might benefit most from the use of this technology.

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APPENDIX 1: AFFILIATIONS AND CONFLICT OF INTEREST DECLARATIONS

Name	Specialty	Location	COI declared
Working Group			
Peter Chung	Radiation Oncologist	Princess Margaret Cancer Centre Toronto, ON,	a
David D'Souza	Radiation Oncologist	London Health Sciences Centre London, Ontario	None declared
Wayne Koll	Radiation Oncologist	Lakeridge health Oshawa Ontario	None declared
Scott Morgan	Radiation Oncologist	University of Ottawa, Division of Radiation Oncology Ottawa, Ontario	None declared
Judy Brown	Health Research Methodologist	Program in Evidence-based Care McMaster University	None declared
Expert Panel (SPACER RRG)			
Michael Brundage	Radiation Oncologist	Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, Ontario	b
Charles Catton	Radiation Oncologist	Princess Margaret Hospital, Toronto, Ontario	c
Libni Eapen	Radiation Oncologist	The Ottawa Hospital Regional Cancer Centre Ottawa, Ontario	None declared
Luluel Khan	Radiation Oncologist	Radiation Oncology University of Toronto Toronto, Ontario	None declared
Andrew Loblaw	Radiation Oncologist	Radiation Oncology University of Toronto Toronto, Ontario	d
George Rodrigues	Radiation Oncologist	London Regional Cancer Program Schulich School of Medicine & Dentistry, University of Western Ontario Kingston, Ontario	None declared

a. Principal investigator in a related area: MRI-Guided HDR Brachytherapy for Prostate Cancer. This study allows the use of rectal spacers within the protocol but is not mandated. The primary objective of the study is to evaluate MR-guided brachytherapy and not the use of rectal spacers; Peer-reviewed article about the use of hydrogel spacer in a Canadian setting. This was not an editorial, commentary or opinion piece. Berlin A, Di Tomasso A, Ballantyne H, Patterson S, Lam T, Sundaramurthy A, Helou J, Bayley A, Chung P. Use of hydrogel spacer for improved rectal dose-sparing in patients undergoing radical radiotherapy for localized prostate cancer: First Canadian experience. Can Urol Assoc J. 2017 Dec;11(12):373-375; Work at Princess Margaret Cancer Centre and the institution has purchased limited quantities of hydrogel spacer for use in selected patients undergoing radiotherapy for prostate cancer both within and outside clinical study settings

b. Genentech Educational Grant $30,000

c. Sit on advisory boards for Abbvie Corp., Bayer Cor. And Sanofi Corp; Canadian PI for CCTG PR13; Provided commentary on the treatment of prostate cancer in JCO, GU site leader at PMH when colleagues received funding from Abbvie for prostate spacer trial

d. Co-owner on a patent of a patient immobilization device for cancer patients (including prostate cancer patients). It is not licensed for use and no royalty agreement has been signed.

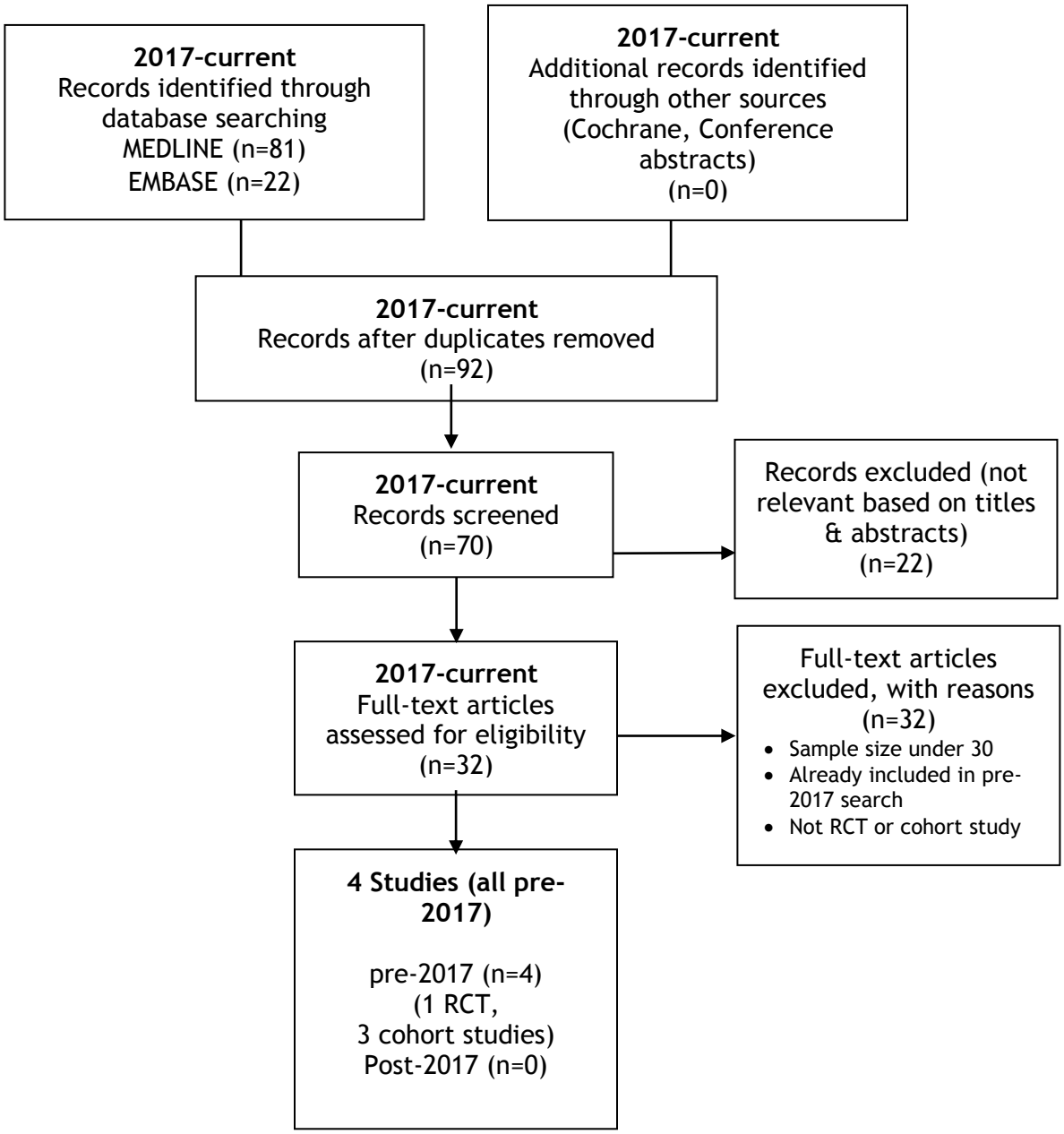
SPACER RRG = biodegradable spacer Insertion during radiotherapy for prostate cancer recommendation report group

APPENDIX 2: LITERATURE SEARCH STRATEGY

Below is the search used in OVID MEDLINE. A similar search was conducted in EMBASE (2017 through Jun 18, 2018), the Cochrane Central Register of Controlled Trials (OVID CCTR: June 2018), and the Database of Abstracts of Reviews of Effects (OVID DARE: 1st quarter 2018).

SEARCH STRATEGY: MEDLINE	
Cancer Terms	1. prostatic neoplasms/
	2. (Prostat* adj4 (Neoplasm* or Cancer* or Carcinom* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or Masses* or Sarcom* or Metastas*)).tw.
	3. 1 or 2
Spacer Inserts	4. Hydrogel/
	5. hydrogel*.tw.
	6. hydrodissect*.tw.
	7. (spacer* or spacing).tw.
	8. ((perirect* or rect* or prostate-rectum or denonvillier* or transperineal*) adj4 space*).tw.
	9. or/4-8
Limiting Terms	10. 3 and 9
	12. 10 or 11
	13. limit 12 to english language
	14, limit 13 to human
	15. limit 14 to yr=2017-Current

APPENDIX 3: PRISMA FLOW DIAGRAM



APPENDIX 4: QUALITY ASSESSMENT

Quality Assessment for Randomized (and Pseudo) Controlled Trials*			
Author	**Entry**	**Judgement**	**Support for Judgement**
Mariados, 2015, Hamstra, 2017 (RCT)	Random sequence generation (selection bias)	Unclear risk	Quote: "…patients were immediately randomized (envelopes opened)."
	Allocation concealment (selection bias)	Unclear risk	Allocation concealment not discussed.
	Blinding of participants and personnel (performance bias)	Low risk	Single blinded study (patients).
	Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors blinded to randomization.
	Incomplete outcome data addressed (attrition bias)	Unclear risk	Low attrition, but only 63% of participates were included in the 3-year follow-up (reasons for not participating not given).
	Selective reporting (reporting bias)	Unclear risk	Only percentages given for some of the outcome's and absolute numbers unclear.
	Other bias	Unclear risk	Study funded by Augmenix (developers of SpaceOAR) and two of the authors are shareholders.
	Overall judgement	**Unclear risk of bias**	
*As determined using the Cochrane collaboration's Tool for Assessing Risk of Bias in Randomized Trials [14]			

Risk of Bias, ROBINS-1* for non-randomized studies		
Author	Entry	Judgement
Pinkawa, 2017	Bias due to confounding	High (non-randomized)
	Bias in selection of participants into the study	Low (consecutive and incident cases used)
	Bias in classification of interventions	Low (data prospectively collected)
	Bias due to departures from intended interventions	Low (departure from intervention not likely)
	Bias due to missing data	Unclear
	Bias in measurement of outcomes	Moderate (some retrospective patient data collected)
	Bias in selection of the reported result	Unclear
	Overall Judgement	**High risk of bias**
Prada, 2009	Bias due to confounding	High (non-randomized)
	Bias in selection of participants into the study	Unclear (unclear if patients consecutive)
	Bias in classification of interventions	Low (bias determined prospectively)
	Bias due to departures from intended interventions	Low (departure from intervention not likely)
	Bias due to missing data	Unclear
	Bias in measurement of outcomes	High (poor quality reporting)
	Bias in selection of the reported result	High (poor quality reporting)
	Overall Judgement	**High risk of Bias**
Te Velde, 2017	Bias due to confounding	High (non-randomized)
	Bias in selection of participants into the study	Unclear (unclear if patients consecutive)
	Bias in classification of interventions	Moderate (intervention determined retrospectively)
	Bias due to departures from intended interventions	Low (departure from intervention not likely)
	Bias due to missing data	Unclear
	Bias in measurement of outcomes	Moderate (retrospective data, blinding unclear)
	Bias in selection of the reported result	Unclear
	Overall Judgement	**High risk of bias**
*As determined using ROBINS (Risk of Bias in Non-randomized Studies-Interventions) tool [23].		