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Hydrogel Spacers for Patients with Prostate Cancer: A Review of Clinical Effectiveness and Cost-Effectiveness

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Abbreviations

3D-CRT	3- dimensional conformal radiation therapy
ACRTN	Australian and New Zealand Clinical Trials Registry
AP	anterior-posterior
CCO	Cancer Care Ontario
CTCAE	Common Terminology Criteria for Adverse Events
EF	erectile function
EPIC	Expanded Prostate Cancer Index Composite
ERB	endorectal balloon
ERBT	external beam radiotherapy
GEL	hydrogel spacer
GI	gastrointestinal
HA	hyaluronic acid
HTA	health technology assessment
HDR	high dose rate
HS	hydrogel spacer
IG-MRT	image guided intensity modulated radiation therapy
IMPT	intensity modulated proton therapy
IMRT	intensity modulated radiation therapy
LR	left-right
MID	minimal clinically important difference
mL	millilitre
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
OAR	organ at risk
PC	prostate cancer
PEG	polyethylene-glycol
PSA	prostate-specific antigen
QoL	quality of life
RCT	randomized controlled trial
RDD	rectal displacement device
RT	radiotherapy or radiation therapy
RTOG	Radiation Therapy Oncology Group
SBRT	stereotactic body radiation therapy
SOH	Space OAR Hydrogel
SR	systematic review
TRUS	transrectal ultrasonography
VMAT	volumetric modulated arc therapy

Context and Policy Issues

Prostate cancer

In 2017, prostate cancer was one of the leading causes of deaths due to cancer in Canadians.[1] It was estimated that 21, 300 Canadians were diagnosed with prostate cancer, and more than 4, 000 died from prostate cancer in 2017.[1] With improved treatment, mortality rates due to prostate cancer are declining.[1] There are several treatment options available for prostate cancer, including surgical resection, chemotherapy, hormonal therapy, and radiotherapy.[1]

Radiotherapy includes several approaches using high-energy rays to destroy cancer cells.[1] Radiotherapy used in prostate cancer can be classified based on the location of the ray sources, types of rays, and position relative to the prostate.[1] When external beam radiation is targeted at the prostate, other adjacent organs are also exposed to radiation.[2] The rectum is located in front of the prostate; because of its vulnerability and the potential for

gastrointestinal adverse effects, the rectum is the dose-limiting organ at risk.[2] For localized prostate cancer, sparing the anterior rectal wall has been emphasized as an important priority to safely deliver effective doses of radiation.[2]

Hydrogel spacer

Spacers can be used to increase the distance between the prostate and the rectum in order to protect the rectum from exposure to radiation.[3] There are several types of spacers, including balloons, plastic rods, and polyethylene-glycol (PEG) hydrogel.[3] PEG hydrogel works like a mesh that contains PEG oligomers and polymers to retain large quantities of water, forming a stable and flexible structure with texture similar to gel.[4] The hydrogel spacers are injected to the space between Denonvilliers fascia and the anterior rectal wall under transrectal ultrasonography (TRUS) guidance.[4] The procedure for injections of the PEG hydrogel takes about 16 minutes from TRUS insertion to TRUS removal.[4] Once placed in the human body, the PEG hydrogel spacer can maintain integrity for three months and is eventually degraded, with the residual excreted in the urine.[4]

The use of hydrogel spacers has demonstrated some clinical effectiveness in the prevention of rectal toxicity to treat patients with localized prostate cancer undergoing radiotherapy,[5] but it is uncertain whether the benefits of hydrogel spacers outweigh the costs and potential harms and whether spacers should be used routinely. This review aims to summarize the available literature to inform an improved understanding of the benefits, harms and costs of hydrogel spacer use.

Research Questions

1. What is the clinical effectiveness of hydrogel spacers for patients with prostate cancer?
2. What is the cost-effectiveness of hydrogel spacers for patients with prostate cancer?

Key Findings

Three systematic reviews, one randomized controlled trial (described within two eligible reports), seven cohort studies, two economic evaluations, and three guidelines were included in this report. Hydrogel spacers were effective in increasing the distance between the prostate and the rectum, and in reducing the radiation dose to the rectum while delivering radiation to the prostate in patients with localized prostate cancer. However, two systematic reviews reported that the clinical benefits were not significant, and were therefore uncertain. One systematic review developed for a health technology assessment did not recommend the routine use of hydrogel spacers for prostate cancer, in consideration of the high costs for their patients. In contrast, three-year follow-up results of a randomized controlled trial indicated that hydrogel spacers were associated with improvements in bowel, urinary and sexual quality of life outcomes. Despite uncertainty, one cost-effectiveness analysis concluded that hydrogel spacers were cost-effective at a willingness to pay threshold of $100,000 in the United States in 2018. One decision analysis concluded that spacer use results in a marginal cost increase and a significant reduction in rectal toxicity. For patients receiving high-dose stereotactic body radiotherapy, the use of hydrogel spacers was found to be cost-effective. The guidelines by Cancer Care Ontario, the National Comprehensive Cancer Network, and the National Institute for Health and Care Excellence recommended the use of hydrogel spacers to reduce rectal toxicity and improve quality of life.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD), Medline, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 01, 2014 and January 24, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with prostate cancer
Intervention	Hydrogel spacers (e.g, Space OAR Hydrogel [SOH], 'rectum sparing prostate radiotherapy')
Comparator	No treatment; other spacer techniques (e.g., other hydrogel spacers, endorectal balloons, prostate locks)
Outcomes	Q1: Clinical Effectiveness Q2: Cost Effectiveness
Study Designs	HTA/Systematic Reviews/Meta-Analyses, Non-Randomized Studies, Randomized Controlled Trials, and Economic Evaluations

HTA = health technology assessment; OAR = organ at risk; SOH = Space OAR Hydrogel

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 were duplicate publications, or were published prior to 2014. Primary studies included within eligible SRs were also excluded. Guidelines employing unclear methods were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using the AMSTAR 2 tool;[6] randomized studies were critically appraised using the Cochrane risk of bias tool;[7] economic studies were assessed using the Drummond checklist;[8] and guidelines were assessed using the AGREE II instrument.[9] Summary scores were not calculated from the assessments of included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 234 citations were identified in the literature search. Following screening of titles and abstracts, 211 citations were excluded and 23 potentially relevant reports from the

electronic database searches were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 10 publications were excluded for various reasons, and 17 publications met the selection criteria for inclusion in this report. These comprised three systematic reviews, one RCT (with results published in two articles), seven non-randomized studies, two economic evaluations, and three evidence-based guidelines. Appendix 1 presents the PRISMA[10] flowchart of the study selection.

Summary of Study Characteristics

Study Design

Three systematic reviews (SRs) were published in 2018, 2018 and 2014 respectively.[3,4,11] Appendix 5 presents the overlap in the included studies i.e., one randomized controlled trial was included by two of the eligible SRs.[3,11] Forero et al. was a SR informing a health technology assessment from the McGill University Health Centre, and included both randomized controlled trials (RCTs) and non-randomized studies.[11] The literature search was conducted on October 4th, 2017.[11] Lawrie et al. reported database searches until 2016 and limited inclusion to RCTs only.[3] Mok et al. did not provide the dates of literature searches;[4] published articles and conference abstracts were eligible for inclusion in the SR.[4] Forero et al. and Mok et al. included six and 11 primary studies, respectively;[3,4,11] all of which were eligible for analysis within this review. While Lawrie et al. included 92 studies in their review,[3] only two of these studies were eligible for analysis within this review.

Primary clinical studies included one RCT (with results reported in two publications),[12,13] five prospective cohort studies,[14-18] and two retrospective cohort studies.[19,20]

Two economic evaluations were conducted in the US.[21,22] Levy et al. adopted the US payer perspective to investigate the cost and effectiveness of hydrogel rectal spacers within five years in a Multistate Markov model.[21] Health utilities and costs were derived from the literature and the 2018 Physician Fee Schedule respectively.[21] Hutchinson et al. did not specify the perspective, and investigated the cost and effectiveness of hydrogel spacers within ten years in a decision tree model.[22] Effectiveness data were based on previous studies and the costs were estimated based on national and institutional data.[22]

Three evidence-based, clinical guidelines by Cancer Care Ontario (CCO), the National Comprehensive Cancer Network (NCCN), and the National Institute for Health and Care Excellence (NICE) were identified.[23-25] CCO adopted the Cochrane Collaboration's tool and ROBINS-I to assess the quality of the literature and the other two groups did not describe the use of quality assessment tools.[23-25] CCO used the AGREE II framework as a strategy to develop clinical guideline and the other two groups did not describe the process of guideline development.[23-25] The recommendations in the CCO were developed and evaluated by a group of radiation oncologists.[23] The methods to generate recommendations were not reported in the other two guidelines.[24,25]

Country of Origin

The SRs were conducted in Canada,[11] the UK,[3], and Switzerland, respectively.[4] The one RCT was conducted in the US.[12,13] Two prospective cohort studies were conducted in the US;[17,18] one in Australia; one in Switzerland,[16] and one in Italy.[14] The two retrospective cohort studies were conducted in Australia[19] and Germany.[20] Two economic evaluations were conducted in the US.[21,22] The CCO guideline was applicable in Canada.[23] The NCCN

guideline was developed and applicable in the US.[24] The NICE guideline was applicable in the UK.[25]

Patient Population

Prostate cancer patients treated with radiation therapy were enrolled in the included studies.[3,4,11-22] In the phase 3 RCT reported in two articles, 222 men with low- or intermediate-risk prostate cancer were treated with radiation therapy.[12,13]

In the cohort study by Hedrick et al., 26 prostate cancer patients treated with proton therapy were enrolled.[18,20] Jones et al. recruited 72 patients diagnosed with low- to intermediate risk prostate cancer and treated with stereotactic body radiation therapy.[17] Wilton et al. recruited 45 patients diagnosed with non-metastatic intermediate- or high-risk prostate cancer and treated with stereotactic body radiation therapy.[19] Picardi et al. included 20 patients diagnosed with localized prostate cancer and treated with image-guided radiation therapy.[16] Juneja et al. recruited 26 patients with prostate cancer and did not specify the type of radiotherapy.[15] Rucinski et al. enrolled 19 prostate cancer patients treated with photons and ions.[20] Ruggieri et al. studied 11 patients with a median age of 73 years diagnosed with low- or intermediate-risk prostate adenocarcinoma and treated with intensity modulated radiotherapy.[14]

In the cost-effectiveness analysis, Levy et al. built the model with data from patients with localized prostate cancer undergoing external beam radiation therapy.[21] The decision analysis in Hutchinson et al. was based on men diagnosed with clinically localized prostate cancer, via prostate-specific antigen screening or digital rectal examination and with a life expectancy greater than ten years.[22]

The CCO guideline is applicable to the patients treated with radiation therapy in Ontario, Canada.[23] The recommendations in the CCO guideline were developed and evaluated by four radiation oncologists.[23] The intended users were radiation oncologists and genitourinary oncologists involved in the management of prostate cancer.[23] The NCCN guideline is designed and evaluated in the USA.[24] The target population and intended users were prostate cancer patients and clinical practitioners respectively.[24] The NICE guideline targets the medical practice in the UK.[25] The recommendations were reached after literature synthesis.[25] The intended users and target population were commissioners and/or providers and prostate cancer patients respectively.[25]

Interventions and Comparators

The hydrogel spacers were compared to no spacers in two SRs[3,11], the RCT,[12,13] three prospective cohort studies,[14-16] one retrospective cohort study,[20] both economic evaluations,[21,22] and the three included clinical guidelines.[23-25] Prostate-rectum spacers, including hydrogel spacers, balloons, and hyaluronic acid spacers, were compared to each other in the SR by Mok et al.[4]

The hydrogel spacers were compared to balloons in two prospective cohort studies.[17,18]

The hydrogel spacers were compared to Rectafix, a plastic rod, in a prospective cohort study by Wilton et al.[19]

Outcomes

The outcomes of interest in two SRs included rectal toxicity measured with the Common Terminology Criteria for Adverse Events (CTCAE) or the modified Radiation Therapy

Oncology Group (RTOG) criteria and quality of life measured with the Expanded Prostate cancer Index Composite (EPIC) questionnaire.[3,11] Forero et al. also evaluated the extent to which a reduction in radiation doses to the rectum was observed.[11] Mok et al. reported the dosimetric effects and potential clinical advantages of hydrogel spacers.[4]

Based on the same RCT first published by Mariados et al. in 2015, Hamstra et al. investigated the sexual quality of life measured with the EPIC questionnaire and Karsh et al. studied rectal and urinary adverse events and quality of life measured with the EPIC questionnaire using extended three-year follow-up data.[12,13]

Four prospective cohort studies,[14,17,19,20] reported dosimetric effects and three investigated prostate motion or displacement.[15,16,18] In addition to the comparison of clinical effectiveness, Jones et al. also examined the comparative costs of balloons and gel.[17]

Both economic evaluations studied the cost and clinical effectiveness of adopting hydrogel spacers.[21,22] The costs were analyzed using US dollars in both studies.[21,22] In the cost-effectiveness study by Levy et al., the time horizons reported were five years.[21] Levy et al. used data from published studies and presented changes in quality-adjusted life years (QALYs) with the spacer costs.[21] In the decision analysis by Hutchinson et al., the time horizon was ten years.[22] Hutchinson et al. compared spacer costs with complications due to rectal toxicity defined by the Modified Radiation Therapy Oncology Group-Late Effects Normal Tissue (RTOG-LENT) scale.[22]

Acute or late toxicities were of interest within the CCO guideline, which included three studies reporting on toxicity and quality of life.[23] In the NCCN guideline, various outcomes were described, but criteria for the outcome selection were not.[24] The key effectiveness outcomes considered in the NICE guideline were reduction of radiation dose to the rectum during radiotherapy, reduction in rectal toxicity, and increase in space and distance between the prostate and rectum.[25]

Additional details regarding the details of included publications are provided in Appendix 2.

Summary of Critical Appraisal

Systematic reviews

There were no protocols published for the three included SRs.[3,4,11] Comprehensive literature searches were described within the methods for the SRs.[3,4,11] Risk of bias in individual studies was assessed;[3,4,11] however, the interpretation of the results did not include consideration of risk of bias.[3,4,11] Lawrie et al. selected the literature, extracted data in duplicate, reported the sources of funding for the included primary studies, meta-analyzed with appropriate statistical methods, and addressed the heterogeneity between included studies, while the other two SRs did not.[3,4,11] Both Forero et al. and Lawrie et al. described the details in the selection of study design, described the included primary studies in detail, and assessed the risk of bias in the primary studies, while Mok et al. did not.[3,4,11]

RCTs

Hamstra et al. and Karsh et al. were reports of the same RCT.[12,13] Neither report described the randomization method used, nor the blinding of outcome assessors.[12,13] Both reports described the same sample sizes and demonstrated a low risk of bias from patient attrition.[12,13] Only the report by Karsh et al. described that patients were blinded and unaware of the treatment allocation.[13] Karsh et al. reported several outcomes, including

quality of life and adverse events, while Hamstra et al. only reported sexual quality of life.[12,13]

Non-randomized studies

The included prospective and retrospective cohort studies used exposure and outcome data documented within surgical records.[14-20] For the dosimetric profiles and prostate motion, no loss to follow-up was reported, and the lengths of follow-up were adequate to assess short-term outcomes.[14-20] Because of the retrospective nature of the study design, the outcome data were available at study initiation in both the Wilton et al. and Rucinski et al. studies;[19,20] thus, the reported results might be at risk of researchers' biases toward certain outcomes in the databases.[19,20] In four studies, the treatment and control groups were comparable,[16-19] while the comparability of different cohorts was neither reported nor confirmed in the other three studies.[14,15,20] Only Picardi et al. and Ruggieri et al. selected the non-exposed cohorts from the same populations.[14,16] Picardi et al. recruited patients from a hospital,[16] while the others used patients from other trials[14,15,17,19,20] or did not report the sources from which patients were recruited or identified.[18]

Economic evaluations

Both reports from Levy et al. and Hutchinson et al. stated the research questions and their economic importance, the rationale for choosing the alternatives, the form of economic evaluations, the sources of effectiveness estimates, primary outcome measures, details of the subjects from whom the valuations were obtained, methods to estimate the quantities and unit costs, currency and price data, details in models, time horizons, approaches to sensitivity analyses, variables informing the sensitivity analyses, answers to the research questions, and conclusions with caveats.[21,22] Levy et al. also described the perspective, details in price and currency adjustments, discount rates, and outcomes in aggregated and disaggregated forms.[21] Hutchinson et al. took productivity into consideration, and reported the resource use along with their unit costs.[22]

Evidence-based guidelines

In the three guidelines from the CCO, NCCN, and NICE, the objectives, health questions, applicable populations, target users, systematic methods for literature searches, criteria to select evidence, strengths and limitations of the evidence, the link between evidence and the recommendations were reported.[23-25] Individuals of all relevant professional groups were involved in the development and the review of the NCCN and NICE guidelines.[24,25] The views and preferences of patients were sought for the NCCN guideline.[24] The strengths and limitations of the evidence were described in the CCO and NICE guideline.[23,25] The methods to formulate the recommendations were mentioned in the NICE guideline.[25] The facilitators and barriers to the guideline application, advice and tools to implement the guideline, and potential resource implications were described in the CCO guideline.[23] There were no procedures to audit or update the guidelines described by any of the guideline authors.[23-25] The competing interests of the guideline development members were recorded in the CCO guideline.[23]

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Clinical Effectiveness of Hydrogel Spacers

Lawrie et al. meta-analyzed two RCTs, characterized by a low-certainty of evidence, and reported no statistically significant differences between patients receiving hydrogel spacers versus those receiving no intervention with regard to acute/late gastrointestinal toxicity or other gastrointestinal symptoms.[3] As it concerned quality of life, results from the two primary studies were inconsistent.[3] The authors concluded that hydrogel spacers for prostate cancer radiation therapy may make little or no difference to gastrointestinal outcomes, such as acute and late gastrointestinal toxicity.[3] In the SR by Forero et al., Spacer OAR, a type of hydrogel spacer, was reported to be significantly associated with lower rectal radiation exposure; nonetheless, authors concluded that it may not contribute to an important reduction in rectal toxicity based on the review of one RCT and three observational studies.[11] Quality of life within the first year of follow-up was not found to be significantly different between Spacer OAR and no spacer and the results of the four primary studies reporting on long-term quality of life were not consistent.[11] Due to the high costs and limited benefits in long-term quality of life, routine use of Spacer OAR at the McGill University Health Centre was not recommended by the authors of the SR.[11] In Mok et al., increased prostate-rectum distance was reported as having a significant association with a lower volume of radiation to the rectum and a reduction in the maximum dose to the rectum.[4]

After three years of follow-up, Hamstra et al. and Karsh et al. both reported a statistically significant reduction in rectal radiation dose and a statistically significant improvement in sexual quality of life, significantly higher scores on seven of 13 items in the sexual domain of the questionnaire.[12,13] In addition, Karsh et al. reported a statistically significant long-term improvement in bowel and urinary quality of life scores in the questionnaire since six months after radiotherapy.[13]

According to the cohort studies, hydrogel spacer placement was not associated with statistically significant changes in prostate motion, compared to no spacer[15,16] or endorectal balloons.[18] Spacer placement was significantly associated with reductions in rectal radiation dose, compared to rectal balloons,[17] and no spacer.[14,20] Rectafix (plastic rods) were found to be clinically equivalent in rectal sparing as hydrogel spacers.[19]

Cost-Effectiveness

In the cost-effectiveness study, Levy et al. reported that hydrogel spacers used in external beam radiation therapy could be cost-effective at a willingness to pay threshold of $100,000, based on the Medicare Physician Fee Schedule in 2018.[21] In the sensitivity analysis, hydrogel spacers were found to be cost-effective in 44.21% of the iterations in the hospital setting at the same willingness-to-pay threshold.[21] In the decision analysis by Hutchinson et al., it was assumed that a reduction in 15-month rectal toxicity would be maintained over 10 years, and the authors concluded that hydrogel spacers for conformal radiation therapy (stereotactic body radiotherapy) were associated with a marginal cost increase and a significant reduction in rectal toxicity, compared to not using spacers.[22] For high-dose stereotactic body radiotherapy, hydrogel spacers were immediately cost-effective.[22] In the sensitivity analysis, the cost-equivalence thresholds were $3,040, $7,990, $33,000, and $162,000 for grade I to IV rectal toxicity.[22]

Guidelines

The Canadian CCO guideline supports the use of biodegradable spacers for patients with localized prostate cancer undergoing radiation therapy in order to reduce toxicity and maintain quality of life.[23] In the NICE guideline, it is recommended to have trained physicians to place hydrogel spacers.[25] However, the NCCN guideline suggests the use of hydrogel spacers when other techniques are insufficient to improve oncologic cure rates and/or reduce side effects.[24] Patients with rectal invasion or visible T3 and posterior extension are not recommended for this procedure.[24]

Appendix 4 presents a table of the main study findings and authors' conclusions.

Limitations

There were several limitations to this review, including the amount and quality of data identified i.e., small sample sizes in the primary studies included in the three SRs,[3,4,11] as well as the included RCT.[12,13] The cohort studies published after 2014 all focused on prostate motion or dosimetric effects;[14-20] thus, the outcomes described in the literature included in this report were limited. In addition to limited evidence, the SRs demonstrated important risks of bias with several methodological limitations identified.[3,4,11] The economic evaluations incorporated several assumptions, including that any observed clinical benefits from hydrogel spacers could be sustained and observed long-term.[22] The conclusion in the local HTA by Forero et al.[11] in Canada seemed to contradict those in the economic evaluations conducted in the US.[22] To better inform the policymakers, the assumptions of the economic evaluations could be verified with and the HTA could be supplemented with the recently published three-year follow-up of the RCT in Hamstra et al. and Karsh et al.[12,13]

Conclusions and Implications for Decision or Policy Making

There were three SRs of very low quality,[3,4,11] one fair-quality RCT,[12,13] two poor-quality retrospective cohort studies,[19,20] five good- to poor-quality prospective cohort studies,[14-18] two economic evaluations,[21,22] and three guidelines included in this review.[23-25] Compared to no spacer, the placement of hydrogel spacers in patients with prostate cancer undergoing radiation therapy led to reductions in rectal radiation dose[4,11,13,17] and was not associated with significant changes in prostate motion,[16,18] Notably, the reduced rectal radiation dose did not translate into clinically important reductions in acute or long-term rectal toxicity, quality of life, and rectal bleeding within the first year of follow-up.[3,11] In consideration of the high costs and limited long-term benefits in quality of life, Forero et al. did not recommend the routine use of hydrogel spacers for patients with prostate cancer receiving radiation therapy in a HTA report produced for the McGill University Health Centre.[11]

The cost-effectiveness analysis by Levy et al. in the US demonstrated that hydrogel spacers could be cost-effective at a willingness to pay threshold of $100,000 in 2018, based on data from the Medicare Physician Fee Schedule.[21] However, these results were subject to uncertainty and additional evidence would better support decision-making.[21] In a decision analysis in the US, hydrogel spacers were associated with a marginal cost reduction and a significant reduction in rectal toxicity.[22] Hutchinson et al. concluded that hydrogel spacer placement was cost-effective for high-dose stereotactic body radiotherapy.[22]

More recently, three-year follow-up results of the RCT (from which earlier findings were also synthesized in two SRs included in this review[3,11]) were published in two articles.[12,13] Both

articles reported significantly improved sexual quality of life due to sufficient erectile function in the spacer group as compared to the no-spacer group.[12,13] In Karsh et al., statistically significant improvements in bowel and urinary quality of life were also reported.[13] This was because the placement of hydrogel spacers was associated with less acute pain, less late rectal toxicity, and improved bowel and urinary quality of life scores since six months of follow-up.[13]

For clinicians, alternatives to hydrogel spacers have been developed, such as plastic rods.[3,19] There are also other no-spacer options available to reduce the adverse effects of radiotherapy for prostate cancer patients, such as the choice of radiotherapy, high-fiber diet, and radiation dose optimization.[3] Consideration of these alternatives may also be important to improve outcomes and quality of life for prostate cancer patients.

Finally, the generation of additional, high-quality studies in this area will be useful to reduce the uncertainty presented by the current evidence base; including, for instance, incorporation of the latest follow-up data generated from the RCT reported by Hamstra et al. and Karsh et al. into SRs, economic evaluations, and guidelines.

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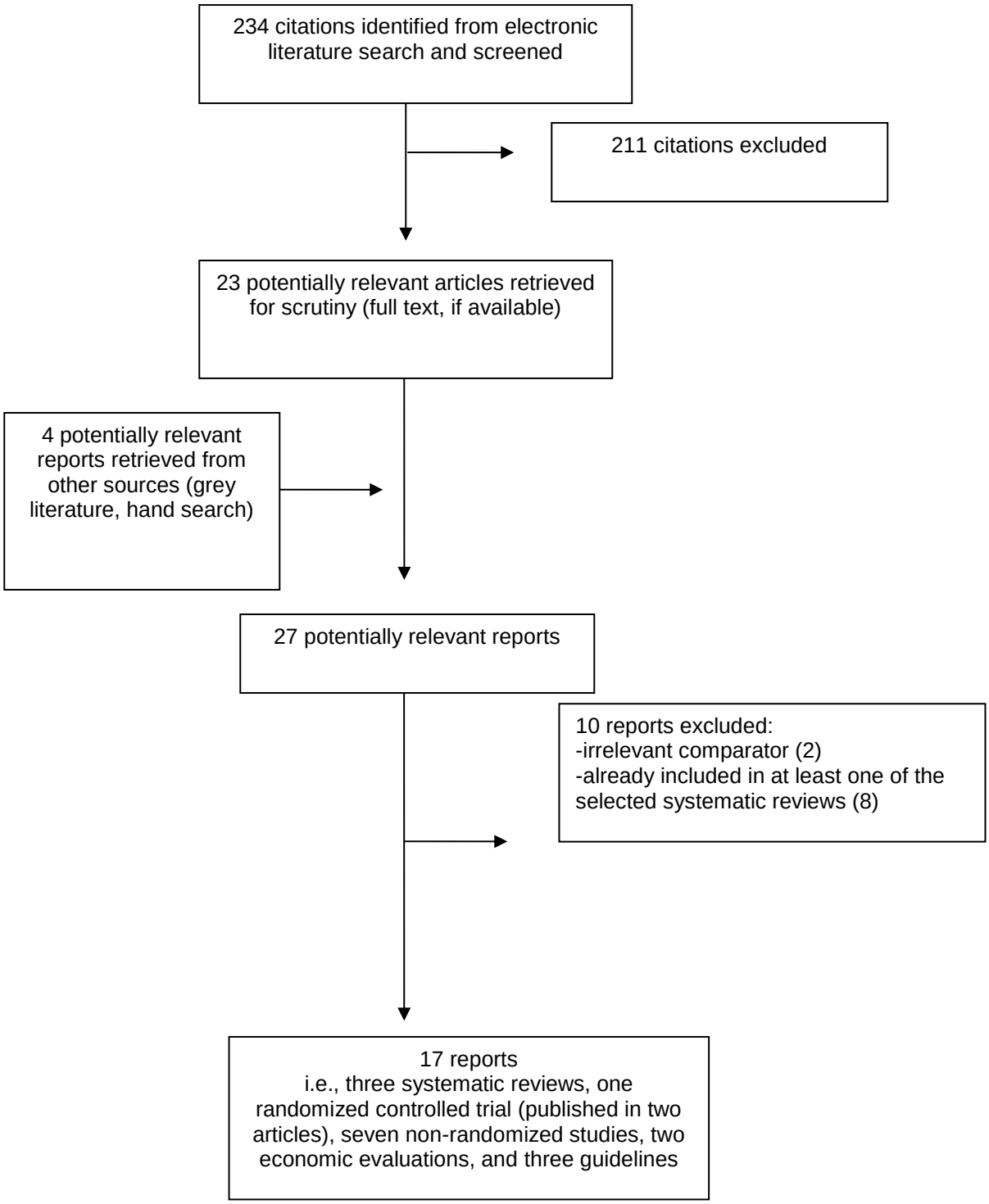
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Forero 2018,[11] Canada	SR for a McGill University Health Centre HTA report Study design searched: RCTs or non-randomized studies Literature search until October 2017	1 RCT and 5 non-randomized studies describing N = 852 patients treated with EBRT	Space OAR versus no spacer Prostate cancer treatment: EBRT	Amount of radiation to the rectum, rectal toxicity and quality of life Follow-up: 3 to 72 months
Lawrie 2018,[3] UK	SR and meta-analysis Study design searched: RCTs Literature search until September 2016	92 RCTs, 2 of which were eligible for inclusion within this report N = 229 and 69 men undergoing RT for prostate cancer	Transperitoneal hydrogel spacer/injection versus no spacer Prostate cancer treatment: all types of pelvic radiation therapy eligible; IG-IMRT (79.2 Gy in 1.8-Gy fractions) in Mariados 2015 and brachytherapy in Prada 2009	Acute GI toxicity, late GI toxicity, other GI symptoms, and quality of life Follow-up: up to 15 months in Mariados 2015 and a median of 26 months in Prada 2009
Mok 2014, Switzerland	SR Study design searched: published articles and conference abstracts Literature search date not reported	11 studies (reported within 12 articles), design not specified by the authors, describing N = 346 patients based on the sample sizes reported in Table 1 and 2 in Mok et al.	Prostate-rectum spacers compared to each other: polyethylene-glycol (PEG) spacers, hyaluronic acid (HA) spacers, biodegradable balloons, and collagen implants identified in the literature searchProstate cancer treatment: IMRT, VMAT, IMPT, 3D-CRT, and HDR monotherapy used in the primary studies	Dosimetric effects, and clinical benefit Follow-up: 3 to 72 months

3D-CRT = 3- dimensional conformal radiation therapy; ERBT = external beam radiotherapy; GI = gastrointestinal; HA = hyaluronic acid; HTA = health technology assessment; HDR = high-dose rate; ; IG-IMRT = image guided intensity modulated radiation therapy; IMPT = intensity modulated proton therapy; IMRT = intensity modulated radiation therapy; PEG = polyethylene-glycol; RCT = randomized controlled trial; RT = radiation therapy; SR = systematic review; UK = United Kingdom; VMAT = volumetric modulated arc therapy

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
RCTs				
Hamstra 2018,[12] Karsh 2018,[13] US	RCT (clinicaltrials.org: NCT01538628), phase 3 trial, multi-centre, patient blinded, allocation concealed	222 patients with National Comprehensive Cancer Network low- or intermediate-risk prostate cancer	Polyethylene glycol (PEG) hydrogels (SpaceOAR System, Augmenix, Inc., Bedford, MA) versus no spacer Prostate cancer treatment: IG-IMRT 79.2 Gy in daily fractions of 1.8 Gy in 44 fractions to the prostate ± seminal vesicles	Hamstra et al.: Sexual quality of life measured by the Expanded Prostate Cancer Index Composite (EPIC): mean scores, the proportion of patients with a minimal clinically important difference (MID), and different items composing the sexual domain Karsh et al.: Acute (0-3 months) and late (3-37 months) rectal and urinary adverse events Expanded Prostate Cancer Index Composite (EPIC) health-related quality of life (QOL) questionnaire at baseline and at 3, 6, 12, 15, and 37 months Median follow-up of 37 months
Non-randomized studies				
Hedrick 2017,[18] US	Prospective cohort study	26 prostate cancer patients treated with proton therapy and an endorectal balloon (n=10) or a hydrogel spacer (n=16) using orthogonal x-rays acquired before and after each treatment field	Endorectal balloons versus hydrogel spacers Prostate cancer treatment: IGRT	Intrafraction prostate motion Follow-up time not reported

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Jones 2017,[17] US	Prospective cohort study, multi-centre [half of the patients from a Phase 1/2 trial of SBRT; half from another phase 2 trial of Pinnacle (Philips North America Corporation, Andover, MA) treatment planning software with photon energies]	72 patients with low- to intermediate risk prostate cancer Exclusion criteria: prostate volumes by ultrasound more than 60 cc (patients allowed up to 9 months of hormonal therapy before SBRT to downsize the prostate gland volume)	Rectal balloons [Pro-Tekt (Donaldson Marphil Medical, Montréal, Québec, Canada)] versus absorbable injectable spacer gel [SpaceOAR (Augmenix, Inc, Waltham, MA)] in stereotactic body radiation therapy (SBRT) for prostate cancer Prostate cancer treatment: SBRT	Dosimetric risk factors for rectal injury; volumetric data from the rectum, bladder, and prostate Costs of balloons and gel Follow-up time not reported
Wilton 2017,[19] Australia	Retrospective analysis of data from a Phase 2 multicentre clinical trial [PROMETHEUS study registered on the Australian and New Zealand Clinical Trials Registry (ACTRN 126150002235380)]	45 patients with non-metastatic intermediate or high-risk prostate cancer	Rectafix (plastic rod) or SpaceOAR Prostate cancer treatment: two SBRT (Stereotactic body radiation therapy) fractions with a RDD (rectal displacement device) in situ totalling either 19 or 20 Gy, using two volumetric modulated arc therapy (VMAT) partial arcs	Rectal radiation doses Follow-up time not reported
Picardi 2016,[16] Switzerland	Prospective cohort study, single centre	20 patients with histologically proven localized prostate cancer treated curatively	Hydrogel spacer gel (SpaceOAR, Augmenix, Waltham, MA, USA) in the recto-prostatic space versus no spacer Prostate cancer treatment: IGRT	Relative displacements between the prostate isocenter based on the position of the center of gravity of the 3 fiducial markers and the bony anatomy: "*quantified in the left-right (LR), anterior-posterior (AP), superior-inferior (SI) axes*" (p. 835) Follow-up time not reported
Juneja 2015,[15] Australia	Prospective cohort study based on 2 prospective clinical trials	26 patients with prostate cancer	Hydrogel (SpaceOAR™) versus no spacer	Intra-fraction motion Follow-up time not reported

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
			Prostate cancer treatment: types of radiation therapy unspecified	
Rucinski 2015,[20] Germany	Retrospective cohort study, two centres	19 patients treated with photons and ions (9 without spacer)	Spacer (SpaceOAR™ System, Augmenix Inc., Waltham, MA, US) versus no spacer Prostate cancer treatment: ion therapy	Dosimetric impact of application of spacer gel on rectal dose Follow-up time not reported
Ruggieri 2015,[14] Italy	Prospective cohort study, single centre	11 patients with prostate adenocarcinoma, low and intermediate risks according to the National Comprehensive Cancer Network (NCCN) Median age = 73 years Age range = 62-78 years	10 mL of Spacer (SpaceOAR™ System, Augmenix Inc., Waltham, MA, US) versus no spacer Prostate cancer treatment: intensity modulated radiotherapy (IMRT) plans	Dosimetric impact of application of spacer gel on rectal dose Follow-up time not reported

ACRTN = Australian and New Zealand Clinical Trials Registry; AP = anterior-posterior; EPIC = Expanded Prostate Cancer Index Composite; IG-IMRT = image guided intensity modulated radiation therapy; IGRT = image guided radiation therapy; IMRT = intensity modulated radiotherapy; LR = left-right; mL = miniliter; MID = minimal clinically important difference; NCCN = National Comprehensive Cancer Network; PEG = polyethylene glycol; QOL = quality of life; RCT = randomized controlled trial; RDD = rectal displacement device; SBRT = stereotactic body radiation therapy; SI = superior-inferior; US = United States of America

Table 4: Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
Levy 2018,[21] US	Cost-effectiveness analysis, 5 years from receipt of radiation therapy, US payer perspective	"*HRS use for reduction in radiation therapy (RT) toxicities in patients with prostate cancer (PC) undergoing external beam RT (EBRT)*" (p. e1)	Patients with localized prostate cancer (PC) undergoing external beam RT (EBRT). Prostate cancer treatment: EBRT	Hydrogel rectal spacers versus no spacer	Multistate Markov model	Health utilities and costs: derived from the literature and the 2018 Physician Fee Schedule respectively, discounted 3% annually	Grade 1 toxicity not different from no toxicity; cost of misplaced hydrogel rectal spacers and associated problems came from clinical expertise after review of case reports for misplaced spacers
Hutchinson 2016,[22] US	Decision analysis, 10-year period across 3 different RT modalities, perspective not specified	"*decision analysis to evaluate the cost effectiveness of a newly Food and Drug Administration approved rectal spacer gel (SpaceOAR, Augmenix) for the reduction of rectal toxicity of prostate radiation therapy (RT)*" (p. 291.e19)	Men diagnosed with clinically localized prostate cancer, cT1 to cT2c, via prostate-specific antigen (PSA) screening or digital rectal examination, and with a life expectancy greater than 10 years Prostate cancer treatment: conformal RT dose escalation, high-dose stereotactic body radiotherapy (SBRT) and low-dose SBRT.	Hydrogel spacers (SpaceOAR, Augmenix Inc., Waltham MA) versus no spacer	Decision tree model (TreeAgePro)	Rectal toxicity (defined by the Modified Radiation Therapy Oncology Group-Late Effects Normal Tissue (RTOG-LENT) scale) rates: from studies on conformal RT dose escalation, high-dose stereotactic body radiotherapy (SBRT) and low-dose SBRT. Rectal toxicity reduction rates	Reduction in Short-term complications: assumed to carry forward to a reduction in long-term toxicity

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
						(baseline reduction 70%): recently published 15 month data using a rectal spacer. Direct and indirect cost estimates for established grades of rectal toxicity: national and institutional costs	

EBRT = external beam radiation therapy; PC= prostate cancer; PSA = prostate-specific antigen; RCT = randomized controlled trial; ; RT = radiation therapy; SBRT = stereotactic body radiotherapy; RTOG-LENT = Radiation Therapy Oncology Group-Late Effects Normal Tissue; US = United States of America

Table 5: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Cancer Care Ontario, 2019[23] Canada						
Radiation oncologists and genitourinary oncologists involved in the management of prostate cancer, patients undergoing radiation treatment for localized prostate cancer.	Biodegradable spacers for prostate cancer treatment	Rectal toxicity, quality of life, bowel function scores	Literature searches with MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews, 2015 to 2018, quantitative and qualitative synthesis	AGREE II framework	Recommendations developed and evaluated by a Working Group consisting of four radiation oncologists	Not reported
National Comprehensive Cancer Network, 2018[24] USA						
Clinical practitioners, patients with prostate cancer	All aspects of prostate cancer diagnosis and treatment, spacers considered	Not specified, but outcomes related to prostate cancer treatment discussed	Literature search with the PubMed data base with grey literature suggested by experts, synthesis methods not mentioned	Not reported	Recommendations developed and evaluated by a group of clinical practitioners	Not reported
National Institute for Health and Care Excellence, 2017[25] UK						
Commissioners and/or providers, patients with prostate cancer	Biodegradable spacers to reduce rectal toxicity during radiotherapy for prostate cancer	Placement success, perirectal space, acute rectal toxicity, t reduction in mean rectal dose volume, bowel quality-of-life scores (assessed using the Expanded	Literature searches with MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases until 25 April 2017, selection process not specified,	Not reported in the methodology article[a]	Recommendations reached after literature synthesis	Not specified in the methodology article[a]

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
		Prostate Cancer Index Composite self-assessment questionnaire), hydrogel absorption	qualitative synthesis			

RCT = randomized controlled trial; UK = United Kingdom; US = United States of America

[a]https://www.nice.org.uk/guidance/ipg590/evidence/overview-final-pdf-4548777229

Appendix 3: Critical Appraisal of Included Publications

Table 6: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR 2 checklist[6]

Strengths	Limitations
Forero et al., 2018[11]	
- PICO components included in the research questions and inclusion criteria for the review - The selection of study design explained - Comprehensive literature search strategy - The characteristics of the included studies described - Risk of bias of the included studies assessed - Review funded by an institute for a health technology assessment report	- Study selection not in duplicate - Data extraction not in duplicate - Review protocol not published *a priori* - Excluded studies not listed - Sources of funding of the included studies not reported - Risk of bias not accounted for when interpreting the results - Heterogeneity not mentioned - Publication bias not assessed
Lawrie et al., 2018[3]	
- PICO components included in the research questions and inclusion criteria for this Cochrane review - The selection of study design explained - Comprehensive literature search strategy - Study selection in duplicate - Data extraction in duplicate - Excluded studies provided - The characteristics of the included studies described - Risk of bias of the included studies assessed - Meta-analysis conducted with adequate statistical methods - Risk of bias accounted for when interpreting the results - Heterogeneity discussed - Publication bias assessed - Sources of funding of the included studies reported	- Review protocol not published *a priori* - Conflict of interest of the review authors not declared
Mok et al., 2014[4]	
- PICO components included in the research questions and inclusion criteria for the review - Comprehensive literature search with Medline - Review funded by an institute for a health technology assessment report	- The selection of study design not explained - Study selection not in duplicate - Data extraction not in duplicate - The characteristics of the included studies not described - Risk of bias of the included studies not assessed - Review protocol not published *a priori* - Excluded studies not provided - Sources of funding of the included studies not reported - Meta-analysis not conducted - Risk of bias not accounted for when interpreting the results - Heterogeneity not mentioned - Publication bias not assessed - Funding sources of this review not mentioned

PICO = population, intervention, comparator, and outcome

Table 7: Strengths and Limitations of Randomized Controlled Trials using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials[7]

Strengths	Limitations
Hamstra et al. and Karsh et al., 2018	
- Patient allocation concealed - Patient attrition reported - Patients blinded - Selective outcome reporting not likely	- Randomization methods not described (Mariados et al. 2015 cited) - Physician blinding not mentioned

Table 8: Strengths and Limitations of Non-Randomized Studies using the Newcastle-Ottawa Scale[26]

Strengths	Limitations
Hedrick et al., 2017[18]	
- Exposure documented in surgical records - Outcome of interest not presenting at start of study - Cohorts from the same area - Outcome documented in surgical records - Follow-up length enough for outcome assessment - No attrition reported	- Patient selection not described
Jones et al., 2017[17]	
- Exposure documented in surgical records - Outcome of interest not presenting at start of study - Cohorts with similar prostate volumes - Outcome documented in surgical records - Follow-up length enough for outcome assessment - No attrition reported	- Patient selected from two different trials
Wilton et al., 2017[19]	
- Exposure documented in surgical records - Cohorts from the same source - Outcome documented in surgical records - Follow-up length enough for outcome assessment - No attrition reported	- Patient selected from a trial - Outcome data available to the authors who conducted the retrospective analysis, constituting a risk of bias
Picardi et al., 2016[16]	
- Patient enrolled in a hospital - Exposure documented in surgical records - Cohorts from the same hospital - Outcome documented in surgical records - Follow-up length enough for outcome assessment - No attrition reported	
Juneja et al., 2015[15]	
- Exposure documented in surgical records - Outcome of interest not presenting at start of study - Outcome documented in surgical records - Follow-up length enough for outcome assessment - No attrition reported	- Patient selected from two different trials - Cohort comparability unclear

Strengths	Limitations
Rucinski et al., 2015[20]	
- Exposure documented in surgical records - Outcome of interest not presenting at start of study - Outcome documented in surgical records - Follow-up length enough for outcome assessment - No attrition reported	- Patient selected from two different trials - Cohort comparability unclear
Ruggieri et al., 2015[14]	
- Exposure documented in surgical records - Outcome of interest not presenting at start of study - Outcome documented in surgical records - Follow-up length enough for outcome assessment - No attrition reported	- Patient selected from two different trials - Cohort comparability unclear

Table 9: Strengths and Limitations of Economic Studies using the Drummond Checklist[8]

Strengths	Limitations
Levy et al., 2018[21]	
- Research questions stated - The economic importance of the research questions mentioned - The viewpoint of the analysis described - Alternatives implied and described as comparators - Cost-effectiveness analysis declared and justified - Sources of effectiveness estimates stated - Primary outcomes stated - Subjects from whom the valuations were obtained given - Methods to estimate costs described - Currency and price data recorded - Details of currency of price adjustments for inflation given - Model specified - Model use and main parameters justified - Time horizon of costs and benefits stated - Discount rates reported - The approach to sensitivity analysis given - Choice of variables for sensitivity analysis justified - Relevant comparator, no spacer, compared - Incremental analysis reported - Major outcomes reported in aggregated and disaggregated forms - The answers to the study questions given - The conclusion from the data reported - Conclusions accompanied by appropriate limitations	- Methods to synthesize multiple estimates not described - Productivity loss not modelled - Quantities of resource use not reported separately from unit costs - Choice of discount rates not justified - The ranges over which the variables were varied not justified
Hutchinson et al., 2016[22]	
- Research questions stated - The economic importance of the research questions mentioned - Alternatives implied and described as comparators - Decision analysis declared and justified - Productivity loss modelled - Quantities of resource use reported separately from unit costs - Sources of effectiveness estimates stated	- The viewpoint of the analysis not described - Details of currency of price adjustments for inflation not given - The ranges over which the variables were varied not justified - Discount rates not reported - No explanation about the absence of discount - Major outcomes not reported in both aggregated and disaggregated forms

Strengths	Limitations
- Primary outcomes stated - Subjects from whom the valuations were obtained given - Methods to estimate costs described - Currency and price data recorded - Model specified - Model use and main parameters justified - Time horizon of costs and benefits stated - The approach to sensitivity analysis given - Choice of variables for sensitivity analysis justified - Relevant comparator, no spacer, compared - Incremental analysis reported - The answers to the study questions given - The conclusion from the data reported - Conclusions accompanied by appropriate limitations	

Table 10: Strengths and Limitations of Guidelines using AGREE II[9]

Item	Guideline		
	CCO, 2019[27]	NCCN, 2018[24]	NICE, 2017 [25]
Domain 1: Scope and Purpose			
1. The overall objective(s) of the guideline is (are) specifically described.	Strongly agreed	Strongly agreed	Strongly agreed
2. The health question(s) covered by the guideline is (are) specifically described.	Strongly agreed	Strongly agreed	Strongly agreed
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Strongly agreed	Strongly agreed	Strongly agreed
Domain 2: Stakeholder Involvement			
4. The guideline development group includes individuals from all relevant professional groups.	Strongly disagreed	Strongly agreed	Strongly agreed
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Strongly disagreed	Strongly agreed	Strongly disagreed
6. The target users of the guideline are clearly defined.	Strongly agreed	Strongly agreed	Strongly agreed
Domain 3: Rigour of Development			
7. Systematic methods were used to search for evidence.	Strongly agreed	Strongly agreed	Strongly agreed
8. The criteria for selecting the evidence are clearly described.	Strongly agreed	Strongly agreed	Strongly agreed
9. The strengths and limitations of the body of evidence are clearly described.	Partly agreed	Strongly disagreed	Strongly agreed
10. The methods for formulating the recommendations are clearly described.	Strongly disagreed	Strongly disagreed	Partly agreed
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Strongly agreed	Strongly agreed	Strongly agreed
12. There is an explicit link between the recommendations and	Strongly agreed	Partly agreed	Strongly agreed

Item	Guideline		
the supporting evidence.			
13. The guideline has been externally reviewed by experts prior to its publication.	Strongly disagreed	Strongly agreed	Strongly agreed
14. A procedure for updating the guideline is provided.	Strongly disagreed	Strongly disagreed	Strongly disagreed
Domain 4: Clarity of Presentation			
15. The recommendations are specific and unambiguous.	Strongly agreed	Strongly agreed	Strongly agreed
16. The different options for management of the condition or health issue are clearly presented.	Agreed	Strongly agreed	Agreed
17. Key recommendations are easily identifiable.	Strongly agreed	Strongly agreed	Strongly agreed
Domain 5: Applicability			
18. The guideline describes facilitators and barriers to its application.	Strongly agreed	Strongly disagreed	Strongly disagreed
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Strongly agreed	Strongly disagreed	Strongly disagreed
20. The potential resource implications of applying the recommendations have been considered.	Strongly agreed	Strongly disagreed	Strongly disagreed
21. The guideline presents monitoring and/or auditing criteria.	Strongly disagreed	Strongly disagreed	Strongly disagreed
Domain 6: Editorial Independence			
22. The views of the funding body have not influenced the content of the guideline.	Strongly agreed	Strongly disagreed	Strongly agreed
23. Competing interests of guideline development group members have been recorded and addressed.	Strongly agreed	Strongly disagreed	Strongly disagreed

CCO = Cancer Care Ontario; NCCN = National Comprehensive Cancer Network; NICE = National Institute for Health and Care Excellence

Appendix 4: Main Study Findings and Authors' Conclusions

Table 11: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Lawrie et al., 2018[3]	
Perineal hydrogel spacers versus no intervention - GI symptom scores: No evidence. - Acute GI toxicity: Low-certainty evidence suggests that "*hydrogel spacers may make little or no difference to acute GI (rectal) toxicity grade 2+ (RR 0.51, 95% CI 0.08 to 3.38; participants = 289; studies = 2; Analysis 7.1) and acute grade 1+ GI toxicity (RR 0.85, 95% CI 0.55 to 1.30; participants = 220; studies = 1; Analysis 7.2)*" (p. 2) - Late GI toxicity: "*Low-certainty evidence suggests that hydrogel spacers may make little or no difference to late GI (rectal) toxicity grade 2+ up to 15 months post-RT (RR 0.16, 95% CI 0.01 to 3.96; participants = 220; studies = 1; Analysis 7.3) and at a median of three years (RR 0.07, 95% CI 0.00 to 1.34, participants = 140, studies = 1; Analysis 7.3). Evidence on late GI toxicity grade 1+ up to 15 months post-RT (RR 0.29, 95% CI 0.07 to 1.19; participants = 220; studies = 1; Analysis 7.4) and at a median of three years (RR 0.24, 95% CI 0.05 to 1.29; participants = 140; studies = 1; Analysis 7.4) is also low certainty.*" (p. 26) - Other GI symptoms: "*Low-certainty evidence suggests that perineal hydrogel (spacer) may make little or no difference to late rectal bleeding (grade 1+) (RR 0.25, 95% CI 0.03 to 1.84; participants = 289; studies = 2; I2 = 0%; Analysis 7.5). Evidence on acute rectal pain is of a very low certainty (RR 0.24, 95% CI 0.08 to 0.78; participants = 220; studies = 1; Analysis 7.6).*" (p. 26) - Quality of life: (1) 'statistically significant' reductions in favour of the hydrogel based on a bowel domain QoL question on rectal pain at six months and 12 months ($P < 0.05$ in Prada 2009); (2) fewer participants in the hydrogel group "*reported declines in QoL relative to those of the control, experiencing 10-point declines at 15 months*" post- RT ($P = 0.087$ in Mariados 2015) (p. 26)	- *"IMRT may be better than 3DCRT in terms of GI toxicity, but the evidence to support this is uncertain"* (p. 2) - *"Low-certainty evidence on balloon and hydrogel spacers suggests that these interventions for prostate cancer RT may make little or no difference to GI outcomes"* (p. 2)
Forero et al., 2018[11]	
SpacerOAR versus no spacer - "*SpaceOAR use does result in lower rectal radiation exposure, this did not translate into an important reduction in rectal toxicity*" (p. ix) - Quality of life within the first year of follow-up: no difference in 4 studies (1 RCT and 3 observational) - Long-term quality of life: inconsistent results across studies. "*At least moderate decline in quality of life in 15% vs. 20% of patients at one year for the SpaceOAR and the control group, respectively. At 36 months, 5% of SpaceOAR vs. 21% of control group patients had at least a moderate decline in QoL*" in the RCT (p. ix)	- *"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 radiotherapy is not-approved"* (p. xv)

Main Study Findings	Authors' Conclusion
Mok et al., 2014[4]	
Polyethylene-glycol hydrogel spacer versus no spacer - Prostate-rectum separation: ranging from 7 to 15 mm - Quality of life: less bowel bother scores in patients receiving implants shortly after completion of RT in 1 study; "*late toxicities at 1 year were mild and uncommon*" in another study (p. 285) - Tolerance: "*In general, the implantation of PR spacers is well tolerated, with an excellent safety profile.*" (p. 285)	- "*The increased PR separation reduces the volume of rectum receiving high doses of irradiation and can reduce the maximum dose delivered to the rectum. The preliminary rectal toxicity data demonstrate minimal acute and early post-RT toxicities, suggesting a potential for reduced long-term toxicities as well*" (p. 287)

3DCRT = 3- dimensional conformal radiation therapy; GI = gastrointestinal; IMRT = intensity modulated radiation therapy; MUHC = McGill University Health Centre; PR = prostate-rectum; QoL = quality of life; RCT = randomized controlled trial; RR = rate ratio; RT = radiation therapy

Table 12: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
RCTs	
Hamstra et al. and Karsh et al., 2018	
Hydrogel spacers versus no spacer **Hamstra et al.** - Dosimetry: Hydrogel reduced penile bulb mean dose, maximum dose, and percentage of penile bulb receiving 10 to 30 Gy (all P < .05) with mean dose indirectly correlated with erections sufficient for intercourse at 15 months (***P*** = .03). - Sexual quality of life: "*statistically nonsignificant differences favoring spacer for the proportion of men with MID and 2× MID declines in sexual QOL with 53% vs 75% having an 11-point decline (P = .064) and 41% vs 60% with a 22-point decline (P = .11)*"; "*At 3 years, more men potent at baseline and treated with spacer had "erections sufficient for intercourse" (control 37.5% vs spacer 66.7%, P = .046) as well as statistically higher scores on 7 of 13 items in the sexual domain (all P < .05)*" (p. e8) **Karsh et al.** - Tolerance: "*Spacer application was well tolerated with a 99% technical success rate*" (p. 39) - Rectal prostate distance: just over 1 cm in the mean additional space - "*Significant rectum and penile bulb radiation dose reduction, resulting in less acute pain, lower rates of late rectal toxicity, and improved bowel and urinary quality of life (QOL) scores from 6 months onward*" (p. 39) - Sexual quality of life: improvements "*observed at 37 months in baseline-potent men, with 37.5% of control and 66.7% of spacer men capable of "erections sufficient for intercourse.""* (p. 39)	**Hamstra et al.** - *"The use of a hydrogel spacer decreased dose to the penile bulb, which was associated with improved erectile function compared with the control group based on patient-reported sexual QOL"* (p. e8) **Karsh et al.** - *"Spacer application significantly reduces rectal radiation dose and results in long-term reductions in rectal toxicity, as well as improvements in bowel, urinary, and sexual QOL."* (p. 39)
Non-randomized studies	
Hedrick et al., 2017[18]	
Endorectal balloons versus hydrogel spacer - There was a statistically significant difference in the mean vector shift between ERB (0.06 cm) and GEL (0.09 cm), (***P*** <	- Prostate motion is clinically comparable between an ERB and a hydrogel spacer, and the time dependencies are similar. A large majority of shifts for both ERB and hydrogel are well within

Main Study Findings	Authors' Conclusion
0.001). - There was no statistical difference between ERB and GEL for shifts greater than 0.3 cm (***P*** = 0.13) or greater than 0.5 cm (***P*** = 0.36)	a typical robust planning margin
Jones et al., 2017[17]	
Injectable spacer gel versus rectal balloon - Dosimetry: injectable spacer gel superior based on "*the maximum dose to the rectum (42.3 vs 46.2 Gy, p < 0.001), dose delivered to 33% of the rectal circumference (28 vs 35.1 Gy, p < 0.001), and absolute volume of rectum receiving 45 Gy (V45Gy), V40Gy, and V30Gy (0.3 vs 1.7 cc, 1 vs 5.4 cc, and 4.1 vs 9.6 cc, respectively; p < 0.001 in all cases)*" (p. 341) - "*There was no difference between the 2 groups with respect to the V50Gy of the rectum or the dose to 50% of the rectal circumference (p = 0.29 and 0.06, respectively). The V18.3Gy of the bladder was significantly larger with the rectal balloon (19.9 vs 14.5 cc, p = 0.003).*" (p. 341)	- "*injectable spacer gel outperformed the rectal balloon in the majority of the examined and relevant dosimetric rectal-sparing parameters*" (p. 341)
Wilton et al., 2017[19]	
Rectafix versus SpacerOAR - "*Rectafix with lower mean doses at 9 out of 11 measured intervals (P = 0.0012)*" (p. 266) - "*A moderate difference with centre 2 plans producing slightly lower rectal doses (P = 0.013)*" (p. 266) - "*Rectafix returned lower mean doses than SpaceOAR (P < 0.001)*" (p. 266) - "*Although all dose levels were in favour of Rectafix, in absolute terms differences were small (2.6–9.0%)*" (p. 266)	- "*Rectafix and SpaceOAR RDD's provide approximately equivalent rectal sparing*" (p. 266)
Picardi et al., 2016[16]	
Hydrogel spacer versus no spacer - "*In patients with or without HS, the overall mean interfraction prostate displacements were 0.4 versus -0.4mm (p = 0.0001), 0.6 versus 0.6mm (p = 0.85), and -0.6mm versus -0.3mm (p = 0.48) for the LR, AP, and SI axes, respectively. Prostate displacements45mm in the AP and SI directions were similar for both groups. No differences in M, ∑ and σ setup errors were observed in the three axes between HS + or HS- patients*" (p. 834)	- "*HS implantation does not significantly influence the interfraction prostate motion in patients treated with RT for prostate cancer. The major expected benefit of HS is a reduction of the high-dose levels to the rectal wall without influence in prostate immobilization*" (p. 834)
Juneja et al., 2016[15]	
Hydrogel spacer versus no spacer - "*The average (±standard deviation) of the mean motion during the treatment for patients with and without hydrogel was 1.5 (±0.8 mm) and 1.1 (±0.9 mm) respectively (p < 0.05)*" (p. 1) - "*The average time of motion >3 mm for patients with and without hydrogel was 7.7 % (±1.1 %) and 4.5 % (±0.9 %) respectively (p > 0.05)*" (p. 1) - "*The hydrogel age, fraction number and treatment time were found to have no effect (R2 < 0.05) on the prostate motion*" (p. 1)	- "*Differences in intrafraction motion in patients with hydrogel and without hydrogel were within measurement uncertainty (<1 mm). This result confirms that the addition of a spacer does not negate the need for intrafraction motion management if clinically indicated.*" (p. 1)

Main Study Findings	Authors' Conclusion
Rucinski et al., 2015[20]	
Spacer gel versus no spacer - "*The application of spacer gel did substantially diminish rectum dose*" (p. 1) - "*Dmax-1 ml on the treatment planning CT was on average reduced from 100.0 ± 1.0% to 90.2 ± 4.8%, when spacer gel was applied*" (p. 1) - "*spacer gel results in a decrease of the daily V90Rectum index, which calculated over all patient cases and CT studies was 10.2 ± 10.4 [ml] and 1.1 ± 2.1 [ml] for patients without and with spacer gel, respectively*" (p. 1)	- "*Application of spacer gel substantially reduced rectal exposure to high treatment dose and, therefore, can reduce the hazard of rectal toxicity in ion beam therapy of PC*" (p. 1)
Ruggieri et al., 2015[14]	
Spacer versus no spacer - "*the increased $D_{2\%}$ was associated with improvements in target coverage, whereas spacer insertion was associated with improvements in both target coverage and rectal V^r_X . By linear correlation analysis, spacer insertion was related to the reductions in rectal V^r_X for $X \geq 28Gy$*" (p. 1)	- "*A slightly increased $D_{2\%}$ or the use of spacer insertion was each able to improve $V^{PTV}_{33:2}$. Their combined use assured $V^{PTV}_{33:2}$ ≥98% to all our patients. Spacer insertion was further causative for improvements in rectal sparing*" (p. 1)

AP = anteriorposterior; CT = computerized tomography; $D_{2\%}$ = near-maximum target dose; ERB = endorectal balloon; GEL = hydrogel spacer; Gy = gray; HS = hydrogel spacer; LR = left-right; MID = minimal clinically important difference; PC = prostate cancer; QOL = quality of life; RCT = randomized controlled trial; RDD = rectal displacement device; RT = radiotherapy; SI = superior-inferior; $V^{PTV}_{33:2}$ = 33.2 Gy to $95% planning target volume; V^r_X = fractions of rectum receiving more than 18, 28 and 32Gy

Table 13: Summary of Findings of Included Economic Evaluations

Main Study Findings	Authors' Conclusion
Levy et al., 2018[21]	
Hydrogel rectal spacers versus no spacer - "*The per-patient 5-year incremental cost for spacers administered in a hospital outpatient setting was $3578, and the incremental effectiveness was 0.0371 QALYs.*"(p. e1) - "*The incremental cost effectiveness ratio was $96,440/QALY for patients with PC undergoing HRS insertion in a hospital and $39,286/QALY for patients undergoing HRS insertion in an ambulatory facility.*" (p. e1) - "*For men with good baseline EF, the incremental cost-effectiveness ratio was $35,548/QALY and $9627/QALY in hospital outpatient and ambulatory facility settings, respectively.*" (p. e1) - One-way sensitivity analyses: "*HRS was found to be cost-effective at a WTP threshold of $100,000 in 44.21% of iterations in the primary analysis in the hospital setting (Fig 3). This same outcome was 71% for men with good baseline EF and 6.6% for the subgroup with poor baseline EF in the hospital outpatient setting*" (p. e5)	- "*Based on the current Medicare Physician Fee Schedule, HRS is cost-effective at a willingness to pay threshold of $100,000. These results contain substantial uncertainty, suggesting more evidence is needed to refine future decision-making.*" (p. e1)
Hutchinson et al., 2016[22]	
Hydrogel rectal spacers versus no spacer - "*The overall standard management cost for conformal RT was $3,428 vs. $3,946 with rectal spacer for an incremental cost of*	- "*The use of a rectal spacer for conformal RT results in a marginal cost increase with a significant reduction in rectal toxicity assuming recently published 15 month rectal toxicity*

Main Study Findings	Authors' Conclusion
$518 over 10 years." (p. 291.e19) - "*For high-dose SBRT, spacer was immediately cost effective with a savings of $2,640 and break even risk reduction at 36%.*" (p. 291.e19) - 1-way sensitivity analysis: "*By varying cost of complications, the threshold values for cost-equivalence were $3,040, $7,990, $33,000, and $162,000 for grades I to IV, respectively.*" (p. 291.e22) - 2-way sensitivity analysis for CRT: "*varying cost and risk reduction of spacer with intercepts at a cost of $2,332 or a reduction of rectal toxicity of 86%.*" (p. 291.e22)	*reduction is maintained over 10 years. For high-dose SBRT it was cost effective*" (p. 291.e19)

EBRT = external beam radiation therapy; EF = erectile function; HRS = hydrogel rectal spacer; PC = prostate cancer; QALY = quality-adjusted life year; SBRT = stereotactic body radiotherapy

Table 14: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Cancer Care Ontario 2019[23]	
- "*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).*" (p. 1)	- "*adequate to support the use of biodegradable rectal spacers for RT in patients with localized prostate cancer.*" (p. 2)
National Comprehensive Cancer Network, 2018[24]	
- "*Endorectal balloons may be used to improve prostate immobilization. Perirectal spacer materials may be employed when the previously mentioned techniques are insufficient to improve oncologic cure rates and/or reduce side effects due to anatomic geometry or other patient related factors, such as medication usage and/or comorbid conditions. Patients with obvious rectal invasion or visible T3 and posterior extension should not undergo perirectal spacer implantation.*" (p. 1)	- Not provided
National Institute for Health and Care Excellence, 2017[25]	
- "*Current evidence on the safety and efficacy of insertion of a biodegradable spacer to reduce rectal toxicity during radiotherapy 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*" (p. 1) - "*The procedure should only be done by clinicians with training in, and experience of, transperineal interventional procedures*" (p. 2) - "*Injecting a biodegradable substance (examples include polyethylene glycol hydrogel, hyaluronic acid and human collagen), or inserting and inflating a biodegradable balloon spacer, in the space between the rectum and prostate is done to temporarily increase the distance between them. The aim is to reduce the amount of radiation delivered to the rectum, and reduce the toxicity to the rectum during prostate radiotherapy.*" (p. 2) - "*The procedure is usually done with the patient under general*	- Not provided

Recommendations	Strength of Evidence and Recommendations
anaesthesia. However, it may be done using local or spinal anaesthesia, depending on local protocols. The patient is placed in the dorsal lithotomy position. With gel injection, a needle is used to insert the gel into the space between the prostate and the rectum using a transperineal approach and transrectal ultrasound guidance. The prostate and the rectal wall are separated using hydrodissection with saline. Once the correct positioning of the needle is confirmed, the biodegradable spacer substance is injected as liquid into the perirectal space. It then polymerises with the saline to form a soft absorbable mass. The spacer degrades slowly over several months. With balloon spacer insertion, a small perineal incision is typically used to insert a dilator and introducer sheath. Using ultrasound guidance, the dilator is advanced towards the prostate base over the needle, which is then removed. A biodegradable balloon is introduced through the introducer sheath and is filled with saline and sealed with a biodegradable plug. The balloon spacer degrades over several months." (p. 22)	

RT = radiation therapy; QOL = quality of life

Appendix 5: Overlap between Included Systematic Reviews

Table 15: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation		
	Lawrie et al., 2018[3]	Forero et al., 2018[11]	Mok et al., 2016[4]
Hamstra 2017		X	
Pinkawa 2017a		X	
Pinkawa 2017b		X	
Te Velde 2017		X	
Whalley 2016		X	
Mariados 2015	X	X	
Strom 2014			X
Song 2013			X
Pinkawa 2012		X	
Weber 2012			X
Pinkawa 2011			X
Prada 2009	X		

Appendix 6: Additional References of Potential Interest

Cohort studies without controls

Chao M, Ho H, Chan Y, et al. Prospective analysis of hydrogel spacer for patients with prostate cancer undergoing radiotherapy. BJU Int. 2018;122(3):427-433.

Chao M, Lim Joon D, Khoo V, et al. The use of hydrogel spacer in men undergoing high-dose prostate cancer radiotherapy: results of a prospective phase 2 clinical trial. World J Urol. 2018;24:24.