EUnetHTA Joint Action 3 WP4

**Rapid assessment of other technologies using the HTA Core Model®
for Rapid Relative Effectiveness Assessment**

BIODEGRADABLE RECTUM SPACERS TO REDUCE TOXICITY FOR PROSTATE CANCER

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Disclaimer

The assessment represents a consolidated view of the EUnetHTA assessment team members and is in no case the official opinion of the participating institutions or individuals.

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External clinical experts (listed below) provided input to the development of the Project Plan and provided advice to the assessment team during the assessment. Mr Daniel Ask (patient partner) provided input to the technical team during the development of the Project Plan and Draft Assessment. The project was advertised on EUnetHTA social media for patient organizations (or individual patients interested) and on each of the dedicated reviewers' and co-authors' networks. We received input from Prostate Scotland. We used this information in our Project Plan including important considerations and patient relevant outcomes. We also reached out to producers of CE-approved biodegradable rectum spacer devices used during prostate cancer radiotherapy. The table below lists the manufacturers that were contacted and provided feedback on the draft project plan and/or the draft assessment.

Ingrid Harboe, information specialist from NIPHNO developed the search strategy and conducted the search. Marco Knelangen, research associate from Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), critically appraised this search strategy and reviewed the information retrieval process.

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Conflict of interest

All authors, co-authors, dedicated reviewers, external experts (health care professionals, patients or patient representatives) involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form, which was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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This document is available on the website of EUnetHTA.

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LIST OF ABBREVIATIONS

3D CRT	Three dimensional Conformal Radiotherapy
5-ARIs	5-Alpha Reductase Inhibitors
ADT	Androgen deprivation therapy
AE	Adverse Event(s)
AS	Active Surveillance
BMI	Body Mass Index
CADTH	Canadian Agency for Drugs and Technologies in Health
CCO	Cancer Care Ontario
CI	Confidence Interval
CS	Clinically significant
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CUR	Health problem and current use of the technology
DRG	Diagnosis Related Groups
EAU	European Association of Urology
EBRT	External-beam radiotherapy
ED	Erectile dysfunction
EFF	Clinical Effectiveness
eLND	Extended lymph node dissection
EORTC	European Organization for Research and Treatment of Cancer
EPIC	Expanded prostate cancer index composite
ePLND	Extended pelvic lymph node dissection
FDA	Food and Drug Administration
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GS	Gleason Score
HA	Hyaluronic Acid
HDR	High dose rate
HIFU	High intensity focused ultrasound
HR	Hazard Ratio
HTA	Health Technology Assessment
IG-IMRT	Image-Guided Intensity-Modulated Radiotherapy
IMRT	Intensity-Modulated Radiotherapy
IPSS	International Prostatic Symptom Score
ISUP	International Society of Urological Pathology
ITP	Innovation and Technology Payment Programme
LBI-HTA	Ludwig Boltzmann Institute for Health Technology Assessment
LDR	Low dose rate
MeSH	Medical Subject Headings
MetS	Metabolic Syndrome

MID	Minimally important difference
MRI	Magnetic Resonance Imaging
MRI TBx	Magnetic Resonance Imaging Targeted Biopsies
NASHA	Non Animal Stabilized Hyaluronic Acid
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence
NIPHNO	Norwegian Institute of Public Health
nRCT	Non-Randomized Control Trial
NSPHMPDB	National School of Public Health, Management and Professional Development
OR	Odds Ratio
PEG	Polyethylene glycol
PICO	Population, Intervention, Comparator, Outcome
POP	Planned and ongoing projects database
PROSPERO	International prospective register for systematic reviews
PSA	Prostate-specific antigen
QoL	Quality of Life
RCT	Randomized Controlled Trial
REA	Relative Effectiveness Assessment
ROBINS-I tool	Risk of Bias in Non-randomized Studies – of Interventions
RR	Relative Risk
RT	Radiation Therapy
RWI	Rectal Wall Infiltration
SAF	Safety
SBRT	Stereotactic body radiotherapy
SEM	Standard error of the mean
SNHTA	Swiss Network for Health Technology Assessment
SRT	Salvage radiotherapy
TEC	Description and technical characteristics of technology
TNM	Tumour node metastasis
TRUS	Transrectal Ultrasound
TURP	Transurethral resection of the prostate
TUR	Transurethral resection
VASPVT	State Health Care Accreditation Agency

SUMMARY OF RELATIVE EFFECTIVENESS OF BIODEGRADABLE RECTUM SPACERS TO REDUCE TOXICITY FOR PROSTATE CANCER

Scope

This assessment addresses the research question whether for adult oncological patients with prostate cancer receiving curative radiotherapy, the application of a biodegradable rectum spacer is more effective and/or safer for rectum toxicity than no rectum spacer. For more information on the scope: Scope.

Introduction

Description of technology and comparators

The technology under assessment concerns biodegradable rectum spacers added to conventional radiotherapy to (temporarily) position the prostate away from the rectum with the aim of reducing the side effects of radiotherapy. At present there are three CE-marked biodegradable spacers in Europe: SpaceOAR™, ProSpace Balloon, and Barrigel™. Radiotherapy is the comparator when used without rectum spacers.

Radiotherapy is one of the mainstays of treatment (surgery being the second) for reducing the risk associated with prostate cancer. It includes several approaches using high-energy rays to destroy cancer cells. It can be classified as external beam radiotherapy (EBRT) or brachytherapy (also called interstitial radiotherapy) depending on the sources of the rays, their type and their position relative to the prostate. In general, greater doses of external beam radiotherapies are associated with better disease control. However, due to the proximity of the prostate to the rectum, greater doses of prostate radiation are also associated with damage to adjacent organs. Side effects of radiation such as bleeding, diarrhoea, incontinence, or rectum ulceration are commonly seen. This makes it desirable to spare organs at risk (i.e. the rectal wall) in order to ensure safer treatment and quality of life.

Biodegradable rectum spacers are inserted into the perirectal space (the space between the prostate and the rectum), increasing the distance between them. Ideally a clinician with training in perirectal insertion will perform the procedure, often an oncologist or urologist. The aim is to reduce the amount of radiation reaching the rectum, thereby reducing the risk of side effects. [B0002][B0004]

Health problem

Prostate cancer is the second most commonly diagnosed cancer in men, with an estimated 1.3 million diagnoses worldwide in 2018, accounting for 15% of all cancers diagnosed. The incidence of prostate cancer diagnosis varies widely between different geographical areas, largely due to the use of prostate-specific antigen (PSA) testing and the aging population. The Guideline for Prostate Cancer elaborated by the European Association of Urology (EAU) includes the three stages of the localized prostate cancer (low-risk, intermediate-risk, high-risk) that are defined as the probability of developing biochemical recurrence in localized prostate cancer. With improved treatment, mortality rates due to prostate cancer are declining. [A0002]

Methods

After an initial search for existing evidence syntheses (i.e. systematic reviews, HTAs), we searched for primary studies in the following databases: Medline (Ovid), AMED, Embase (Ovid), Epistemonikos, and Cochrane Central Register of Controlled Trials. We also searched trial registry records at ClinicalTrials.gov and WHO ICTRP, Devices@FDA, the American Society of Clinical Oncology conference abstracts, and the Radiation Therapy Oncology Group clinical trials protocols. The detailed search strategy is available in Appendix 1. In addition to the systematic search, we also considered information derived from clinical practice guidelines, information from

a general literature search and input from clinical experts, and manufacturers to complete the technical characteristics of the technology (TEC) and current use of the technology (CUR) domains.

Two reviewers independently screened studies retrieved through the literature search against the predefined criteria. One reviewer used a pre-established form to extract data from the selected studies, with a detailed review by another reviewer. For risk of bias assessment, two reviewers independently appraised the biases at study level, using the Cochrane Risk of Bias tool [1] for randomized control trials (RCT) and the ROBINS-I tool (Risk of Bias in Non-randomized Studies – of Interventions) [2] for non-randomized studies. To rate the certainty of the evidence for each outcome, we used GRADE (Grading of Recommendations, Assessment, Development and Evaluation)[3]. For the TEC and CUR domains, no quality tool was used. Clinical experts, Prostate Scotland, and the SpaceOAR™ and Barrigel™ manufacturers reviewed the second draft and last draft.

In accordance with the GRADE approach, we graded the importance of each outcome through a structured process. To interpret the magnitude of effect sizes, we screened the literature to identify accepted standards for minimally important differences (MID) for the outcomes that we selected in this assessment.

Results

Available evidence

We identified one RCT [4], several companion studies [5-7] from the same clinical trial (NCT01538628) [8] and one nRCT (non-randomized control trial) [9]. The RCT evaluated the effectiveness and safety of SpaceOAR™+Radiotherapy (RT) vs radiotherapy alone, while the nRCT included three groups (i.e. gel+RT, balloon+RT and radiotherapy alone). Both studies were deemed to be at high risk of bias overall. We also identified 15 trial registry records including biodegradable rectum spacers which are at different statuses (e.g. completed, ongoing, recruiting). The main reasons for excluding studies were study design, type of intervention or comparator, no inclusion of outcome of interest, wrong population, no data provided for individuals with spacers, or no full text available.

Clinical effectiveness

The included studies did not measure mortality [D0001], morbidity [D0005/D0006], patient satisfaction [D0017], overall survival and overall quality of life [D0012].

Rectal Toxicity
Two studies assessed rectal and urinary/genitourinary toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) [10].

Acute rectal toxicity

- in the RCT at 3 months follow-up, the risk of grade 1 rectal toxicity was 23% lower in the SpaceOAR™ +RT group (RR 0.77, 95% CI 0.50 to 1.19; 1 study, 220 participants; low certainty of evidence) and the risk of developing grade 2 or greater was 9% lower in the SpaceOAR™ +RT group compared to the RT group (RR 0.91, 95% CI 0.23 to 3.5; 1 study, 220 participants; low certainty of evidence). The differences were not statistically significant (null value of 1 lies in the 95% CI). No grade 3 or 4 toxicities were reported in the intervention; one grade 3 and no grade 4 were reported in the RT group.
- evidence from the nRCT is very uncertain about the effect of gel+RT or balloon+RT in acute rectal toxicity up to 3 months; the risk of developing grade 1 was 60% lower in the RT group (RR 1.58, 95% CI 0.34 to 7.60; 1 study, 49 participants; very low certainty of evidence) and 64% lower in the RT group vs balloon+RT (RR 1.64, 95% CI 0.35 to 7.60; 1 study, 48 participants; very low certainty of evidence). The differences were not statistically significant (null value of 1 lies in the 95% CI). No other grades were reported in the study.

Late rectal toxicity

- in the RCT at 15 months follow-up, the risk of grade 1 rectal toxicity was 66% lower in the SpaceOAR™+RT group compared to RT alone (RR 0.34, 95% CI 0.08 to 1.48; 1 study, 220 participants; low certainty of evidence). The difference was not statistically significant (null value of 1 lies in the 95% CI). There was 1 grade 3 case in the RT group and no grades 2 or 4 reported.

Acute and Late rectal toxicity (cumulative incidence)

- evidence from the RCT is very uncertain about the effect of SpaceOAR™ +RT in acute and late rectal toxicity up to 3 years. Results show patients in the intervention group at any time point during the study period were 76% less likely to present grade 1 rectal toxicity when compared to RT alone (HR 0.24, 95% CI 0.06 to 0.97; 1 study, 140 participants; very low certainty of evidence). The difference between SpaceOAR™ +RT vs RT alone was statistically significant (p<.03). The HR was not presented for grades ≥2. There was 1 case of grade 3 toxicity in the RT group, and no cases of grade 4 reported.

Urinary Toxicity

Acute urinary toxicity

- in the RCT at 3-months follow-up: the risk of developing grade 1 was 2% lower in the RT group (RR 1.03, 95% CI 0.87 to 1.21; 1 study, 220 participants; low certainty of evidence) and the risk of developing grade ≥2 urinary toxicity was 3% lower in the SpaceOAR™ +RT group (RR 0.97, 95% CI 0.81 to 1.18; 1 study, 220 participants; low certainty of evidence). The differences between intervention and control groups for all grades of urinary toxicity were not statistically significant. No grades 3 or 4 were reported.
- evidence from the nRCT is very uncertain about the effect of gel+RT or balloon+RT in acute urinary toxicity up to 3 months. Results from the nRCT suggest the risk of developing grade 2 genitourinary toxicity was 39% lower in the RT group (RR 1.39, 95% CI 0.57 to 3.38; 1 study, 49 participants; very low certainty of evidence) but 21% lower in the balloon+RT (RR 0.78, 95% CI 0.28 to 2.22; 1 study, 48 participants; very low certainty of evidence). The differences between groups were not statistically significant (null value of 1 lies in the 95% CI). No grades 3 or 4 were recorded.

Late urinary toxicity

- in the RCT at 15 months, the risk of developing grade 1 urinary toxicity was 35% lower in the SpaceOAR™ +RT group (RR 0.65, 95% CI 0.15 to 2.85; 1 study, 220 participants; low certainty of evidence) and the risk of developing grade 2 or greater was 57% lower in the control group (RR 1.57, 95% CI 0.44 to 5.53; 1 study,220 participants; low certainty of evidence). The differences between SpaceOAR™ +RT and RT for grade 1 or grade ≥2 urinary toxicity were not statistically significant (null value of 1 lies in the 95% CI). No grade 3 or 4 urinary toxicities were reported.

Acute and late urinary toxicity (cumulative incidence)

- evidence from the RCT is very uncertain about the effect of SpaceOAR™ +RT in acute and late urinary toxicity up to 3 years. Participants in SpaceOAR™ +RT group at any time point during the study period were 64% less likely to present grade 1 urinary toxicity (HR 0.36, 95% CI 0.12 to 1.1; 1 study, 140 participants; very low certainty of evidence) but the risk for grade ≥2 was 22% lower in the RT group (HR 1.22, 95% CI 0.40 to 3.72; 1 study, 140 participants; very low certainty of evidence). The differences between SpaceOAR™ +RT and RT were not statistically significant (null value of 1 lies in the 95% CI).

Quality of Life (QoL)

The RCT reported on QoL outcome [5-7, 11, 12]. The outcome was assessed according to the Expanded Prostate Cancer Index Composite (EPIC) 50 item scale [13], in which higher values indicate better QoL. The RCT reported on three summary domains: bowel, urinary, and sexual. Data were presented for 3, 6, 12, 15 and 36 months. [D0013] Proportions of men experiencing minimally important differences (declines) in all three QoL summary domains at 36 months were 2.5% with SpaceOAR™ +RT vs 20% in RT (p=.002; difference relative to control 88%).

- Bowel QoL: results suggest SpaceOAR™ +RT may improve bowel QoL (p=.002) over the entire follow-up period (1 study, 140 participants; very low certainty of evidence) but the evidence is uncertain.
- Urinary QoL: results suggest SpaceOAR™ may have little to no effect on urinary QoL (p=.13) over the study follow-up period (1 study-, 140 participants; very low certainty of evidence), but the evidence is very uncertain.
- Sexual QoL: results suggest SpaceOAR™ may have little to no effect on sexual QoL (p=.6) over the entire study period (1 study, 140 participants; very low certainty of evidence), but the evidence is very uncertain.

Rectal Dose

The proportion of SpaceOAR™ +RT patients who achieved ≥25% reduction in rectal volume receiving an isodose of 70 Gy (rV70) was 97% (1 study, 220 participants; low certainty of evidence). When compared to RT alone, SpaceOAR™ +RT may result in a reduction in rV70 rectal dose to the rectum (p<.0001).

When compared to RT alone, gel+RT and balloon+RT may reduce the dose to the rectum, but the evidence is uncertain (p<.001, 1 study, 78 participants; very low certainty of evidence).

Distance between rectum and prostate

The RCT reported mean perirectal distance between the posterior prostate capsule and the anterior rectal wall on axial mid-gland T2-weighted Magnetic Resonance Imaging (MRI). Results suggest SpaceOAR™ increases perirectal distance by 1.1cm; baseline value was 0.16±0.22cm and after insertion 1.26±0.39cm; SpaceOAR™+RT mean perirectal distance was 0.9±0.59cm at three months (1 study, 149 participants; low certainty of evidence).

PSA relapse

The evidence suggests the addition of SpaceOAR™ while receiving RT, when compared to RT alone, may result in little to no difference in PSA relapse at 12 and 15 months post-radiotherapy (12 months p=.96 and 15 months p=.78; 1 study, 220 participants: low certainty of evidence). The outcome was not reported at 36 months.

Safety

Procedural adverse events were scored as definitely, possibly, unlikely, or definitively not related to the procedure. Only those scored by the blinded adjudicating panel as definitely or possibly were included as adverse events. Insertion of SpaceOAR™ Hydrogel may increase adverse events slightly, i.e. rectal wall infiltration was seen in 9 (6%) patients [C0008]; 10% of spacer patients reported transient grade 1 (n=6.7%) not requiring medication or grade 2 events (n=3.3%) requiring medication; 2/149 spacer patients had no SpaceOAR™ Hydrogel present after application, hydrogel was injected beyond the prostate in 1 patient. Evidence comes from 1 study with148 participants; low certainty of evidence. There were no adverse events attributed to the hydrogel itself.

The studies did not measure severity of harms over time and setting [C0004], which patient groups are more susceptible to or likely to be harmed by the use of the technology [C0005] or address the kind of data/records and/or registry needed to monitor use of the technology. [B0010]

Ethical, organizational, patient and social and legal aspects (if applicable)

The use of biodegradable rectum spacer devices for prostate cancer may require special ethical considerations because of its invasiveness and the conditions of the insertion procedure. From an organizational perspective, it may require some changes due to its insertion prior to radiotherapy, the need for an anaesthesiologist and procedural expertise. The procedure should only be done by clinicians with training in, and experience of, transperineal interventional procedures. From a legal perspective, treatment with biodegradable rectum spacers does not have any major specific risk.

Upcoming evidence

We identified 15 trial registry records including a biodegradable rectum spacer. Of these, n=3 are completed. The status of the others are n=3 “unknown”, n=1 “suspended”, and n=3 “no longer recruiting”. There were n=2 “active, not recruiting” and n=3 “recruiting”. It is not known when these studies will be completed. A detailed table of trial registry records is available in Appendix 1-Table A3.

Reimbursement (optional)

The technology is reimbursed in 4 (France, Germany, Italy, England) out of 12 countries (Austria, Croatia, Hungary, Italy (different region from above), Lithuania, Poland, Scotland, Switzerland, and the Netherlands) for which we have information available. [A0021]

Table 0-1: Summary of findings table of biodegradable rectum spacers for prostate cancer radiotherapy

Biodegradable rectum spacers compared with radiotherapy for prostate cancer						
Patient or population: adults with T1 and T2 stage localized prostate cancer **Settings: Tertiary care** **Intervention: Transperineal hydrogel or balloon plus radiotherapy** **Comparison: Radiotherapy alone**						
Outcomes	**No. of Patients**		**Relative Effect (95% CI)**	**Absolute Effect (95% CI)**	**Importance and Study Certainty of evidence (GRADE)**	**Comments**
	Spacer+RT	**RT alone**				
Rectal Toxicity[1]	**(n=148)**	**(n=71)**				
Acute (grade 1) – 3 months	34	20	RR 0.77 (0.50 to 1.19)	94 fewer per 1000 (from 204 fewer to 78 more)	Critical 1 RCT ⨁⨁⊖⊖ LOW[2,3]	
Acute (grade ≥2) – 3 months	6*	3**	RR 0.91 (0.23 to 3.5)	6 fewer per 1000 (from 47 fewer to 152 more)		*no grade 3 or 4 toxicity reported **one grade 3 case, no grade 4 reported
Late (grade 1) – 15 months	3	4	RR 0.34 (0.08 to 1.48)	40 fewer per 1000 (from 56 fewer to 29 more)		
Late (grade≥2)[4] – 15 months	0	1*	RR 0.15 (0.01 to 3.71)	13 fewer per 1000 (from 15 fewer to 41 more)		*one grade 3 case, no grade 4 reported
Acute and Late (grade 1) – median 3 years	2	4	HR 0.24, 95% CI 0.06 to 0.97	Not able to calculate	Critical 1 RCT ⨁⊖⊖⊖ VERT LOW[2,3,5]	Loss to follow up 37% (spacer+RT n=54 and RT alone n=25)
Acute and Late (grade ≥2) – median 3 years	0	3	HR not available	Not able to calculate		
Rectal Toxicity (Wolf 2015)[1]						
	(Gel n=30, balloon n=29)	**(n=19)**				
Acute rectal toxicity (grade 1) – 3 months	5	2	RR 1.58 (0.34 to 7.60)	61 more per 1000 (from 69 fewer to 695 more)	Critical 1 nRCT	Gel vs RT – no grade 2-3 toxicity

Biodegradable rectum spacers compared with radiotherapy for prostate cancer						
Patient or population: adults with T1 and T2 stage localized prostate cancer **Settings: Tertiary care** **Intervention: Transperineal hydrogel or balloon plus radiotherapy** **Comparison: Radiotherapy alone**						
Outcomes	**No. of Patients**		**Relative Effect (95% CI)**	**Absolute Effect (95% CI)**	**Importance and Study Certainty of evidence (GRADE)**	**Comments**
	Spacer+RT	**RT alone**				
	5		RR 1.64 (0.35 to 7.60)	67 more per 1000 (from 68 fewer to 695 more)	⊕⊖⊖⊖ Very Low[3,6]	Balloon vs RT – no grade 2-3 toxicity
Urinary Toxicity[1]						
	(n=148)	**(n=71)**				
Acute (grade 1) – 3 months	78	33	RR 1.03 (0.87 to 1.21)	25 more per 1000 (from 107 fewer to 173 more)	Critical 1 RCT ⊕⊕⊖⊖ LOW[2,3]	
Acute (grade ≥2) – 3 months	56	32	RR 0.97 (0.81 to 1.18)	25 fewer per 1000 (from 156 fewer to 148 more)		*no grade 3 or 4 toxicity reported
Late (grade 1) – 15 months	4	3	RR 0.65 (0.15 to 2.85)	15 fewer per 1000 (from 36 fewer to 75 more)		
Late (grade ≥2) – 15 months	10*	3*	RR 1.57 (0.44 to 5.53)	25 more per 1000 (from 23 fewer to 196 more)		*no grade 3 or 4 toxicity reported
Acute and Late (grade 1) – median 3 years	4	7	HR 0.36 (0.12 to 1.1)	Not able to calculate	Critical 1 RCT ⊕⊖⊖⊖ VERY LOW[2,3,5]	Loss to follow up 37% (spacer+RT n=54 and RT alone n=25)
Acute and Late (grade ≥2) – median 3 years	Not reported	Not reported	HR 1.22 (0.40 to 3.72)	Not able to calculate		
Genitourinary Toxicity (Wolf 2015)						
	(n=30 gel, n=29 balloon)	**(n=19)**				

Biodegradable rectum spacers compared with radiotherapy for prostate cancer						
Patient or population: adults with T1 and T2 stage localized prostate cancer **Settings: Tertiary care** **Intervention: Transperineal hydrogel or balloon plus radiotherapy** **Comparison: Radiotherapy alone**						
Outcomes	**No. of Patients**		**Relative Effect (95% CI)**	**Absolute Effect (95% CI)**	**Importance and Study Certainty of evidence (GRADE)**	**Comments**
	Spacer+RT	**RT alone**				
Acute – grade 2	11	5	RR 1.39 (0.57 to 3.38)	103 more per 1000 (from 113 fewer to 626 more)	Critical 1 nRCT ⨁⊖⊖⊖ Very Low[3,6]	Gel or Balloon vs RT – no grade 3 toxicity
	6		RR 0.78 (0.27 to 2.12)	58 fewer per 1000 (from 192 to 295 more)		
Bowel Quality of Life - assessed with EPIC 0-100 – greater values are better						
Summary Score: results suggest SpaceOAR™ +RT may improve bowel QoL (p = .002) over the entire follow up period (1 study, 220 participants; very low certainty of evidence) but the evidence is uncertain.						
Minimal Clinical Difference – 5 point decline						
Bowel QoL 3 months	73/148 (49%)	32/71 (46%)	RD 0.05, 95% CI -0.09 to 0.19	5 more people in intervention reported 5 point decline	Critical 1 RCT ⨁⨁⊖⊖ LOW[2,3]	
Bowel QoL 15 months	36/148 (24%)	24/71 (34%)	RD -0.09, 95% CI -0.22 to 0.04	9 less people in intervention reported 5 point decline		
Bowel QoL 36 months	13/94 (14%)	19/46 (41%)	OR 0.28, 95% CI 0.13 to 0.63*	27% less patients in the intervention experiencing 5 point decline	1 RCT ⨁⊖⊖⊖ VERY LOW[2,3,5]	
Minimal Clinical Difference X2 – 10 point decline						
Bowel QoL 3 months	50/148 (34%)	23/71 (32%)	RD 0.02, 95% CI -0.11 to 0.15	2 more people in the intervention reported 10 point decline	Critical 1 RCT	

Biodegradable rectum spacers compared with radiotherapy for prostate cancer						
Patient or population: adults with T1 and T2 stage localized prostate cancer **Settings: Tertiary care** **Intervention: Transperineal hydrogel or balloon plus radiotherapy** **Comparison: Radiotherapy alone**						
Outcomes	**No. of Patients**		**Relative Effect (95% CI)**	**Absolute Effect (95% CI)**	**Importance and Study Certainty of evidence (GRADE)**	**Comments**
	Spacer+RT	**RT alone**				
Bowel QoL 15 months	17/148 (11%)	15/71 (21%)	RD -0.09, 95% CI -0.20 to 0.01	10 fewer people in the intervention reported a 10 point decline	⊕⊕⊖⊖ LOW[2,3]	
Bowel QoL 36 months	5/94 (5%)	7/46 (16%)	OR 0.30, 95% CI 0.11 to 0.83	16% fewer patients in the intervention reported 10 point decline	1 RCT ⊕⊖⊖⊖ VERY LOW[2,3,5]	
Urinary Quality of Life - assessed with EPIC 0-100 – greater values are better						
Summary Score: Results suggest SpaceOAR™ may have little to no effect on urinary QoL (p=.13) over the study follow up period (1 study, 220 participants; very low certainty of evidence); the evidence is very uncertain.						
Minimal Clinical Difference – 6 point decline						
Urinary QoL 3 months	97/148 (65%)	42/71 (60%)	RD 0.07, 95% CI -0.07 to 0.21	7 more people in the intervention reported 6 point decline	Critical 1RCT ⊕⊕⊖⊖ LOW[2,3]	
Urinary QoL 15 months	32/148 (22%)	15/71 (21%)	RD 0.01, 95% CI -0.11 to 0.12	There was no difference in the number of patients reporting 6 point decline		
Urinary QoL 36 months	28/94 (30%)	8/46 (17%)	OR 0.41, 95% CI 0.18 to 0.95	13% fewer participants in the intervention reported 6 point decline	Critical 1 RCT ⊕⊖⊖⊖ VERY LOW[2,3,5]	
Minimal Clinical Difference x 2 – 12 point decline						

Biodegradable rectum spacers compared with radiotherapy for prostate cancer						
Patient or population: adults with T1 and T2 stage localized prostate cancer **Settings: Tertiary care** **Intervention: Transperineal hydrogel or balloon plus radiotherapy** **Comparison: Radiotherapy alone**						
Outcomes	**No. of Patients**		**Relative Effect (95% CI)**	**Absolute Effect (95% CI)**	**Importance and Study Certainty of evidence (GRADE)**	**Comments**
	Spacer+RT	**RT alone**				
Urinary QoL 3 months	70/148 (47%)	34/71 (49%)	RD 0.00, 95% CI -0.14 to 0.14*	There was no difference in the number of patients reporting 12 point decline	Critical 1RCT ⨁⨁⨀⨀ LOW[2,3]	
Urinary QoL 15 months	14/148 (9%)	9/71 (12%)	RD -0.03, 95% CI -0.12 to 0.06	3 fewer patients in the intervention reported 12 point decline		
Urinary QoL 36 months	22/94 (23%)	4/46 (8%)	OR 0.31, 95% CI 0.11 to 0.85*	15% fewer participants in the intervention reported 12 point decline	1 RCT ⨁⨀⨀⨀ VERY LOW[2,3,5]	
Sexual Quality of Life – assessed with EPIC 0-100 – greater values are better						
Summary Score: results suggest SpaceOAR™ may have little to no effect on sexual QoL (p=.6) over the entire study period (1 study, 140 participants; very low certainty of evidence), but the evidence is very uncertain.						
36 months	94	46	Not estimable	Sexual composite over time p=0.59	Critical 1 RCT ⨁⨀⨀⨀ VERY LOW[2,3,5]	
Rectal Dose						
rV70 Mean ± SD	148	71	--	--	Critical 1 RCT ⨁⨁⨀⨀ LOW[2,3]	97%intervention patients reached ≧25% reduction in rV70
Isodose	Gel 30 Balloon 29	19	95% isodose	38% and 63% less	Critical	g-gel, b-balloon c control

Biodegradable rectum spacers compared with radiotherapy for prostate cancer						
Patient or population: adults with T1 and T2 stage localized prostate cancer **Settings: Tertiary care** **Intervention: Transperineal hydrogel or balloon plus radiotherapy** **Comparison: Radiotherapy alone**						
Outcomes	**No. of Patients**		**Relative Effect (95% CI)**	**Absolute Effect (95% CI)**	**Importance and Study Certainty of evidence (GRADE)**	**Comments**
	Spacer+RT	**RT alone**				
			10.9 cm^2 -g. 17.6 cm^2c 6.6 cm^2 -b 85% isodose 18.3 cm^2-g. 24.1 cm^2 c 13.2 cm^2-b 60% isodose 34.4 cm^2-g 38.3 cm^2 c 29.7 cm^2-b	24% and 42% less 10% and 22% less	1 nRCT ⊕⊖⊖⊖ Very Low[3,6]	
Distance between rectum and prostate – baseline, post-insertion, 3 months						
Mean perirectal distance (mm)	149	--	Not estimable	Not estimable	Important 1 RCT ⊕⊕⊖⊖ LOW[2,3]	1.6±2.2 mm, 12.6±3.9 mm, 9±5.9 mm
PSA relapse – baseline, 12 and 15 months						
Ng/mL – 12 months and 15 months	148	71	Not estimable	Not estimable	Important 1 RCT ⊕⊕⊖⊖ LOW[2,3]	Values only presented as means (no SD available), no data for 36 months available.
Overall Survival – outcome not measured						
Adverse events related to the technology						

Biodegradable rectum spacers compared with radiotherapy for prostate cancer						
Patient or population: adults with T1 and T2 stage localized prostate cancer **Settings: Tertiary care** **Intervention: Transperineal hydrogel or balloon plus radiotherapy** **Comparison: Radiotherapy alone**						
Outcomes	**No. of Patients**		**Relative Effect (95% CI)**	**Absolute Effect (95% CI)**	**Importance and Study Certainty of evidence (GRADE)**	**Comments**
	Spacer+RT	**RT alone**				
Deaths related to adverse events, grade 5	207	91	There was no (device) death related to adverse events reported in these studies		Critical 1 RCT and 1 nRCT	
Adverse events, grades 3-4	207	91	There was no (device) grades 3-4 related to adverse events reported in these studies			
Adverse events grades 1-2 [1]	148	71	• no unanticipated SpaceOAR™ related adverse events; • 10% of the spacer patients had mild transient procedural adverse events • n=10 events requiring no medication • grade 2 events treated with medication included mild lower urinary tract symptoms and hypotension, and moderate perineal pain. • no implant infections, rectal wall ulcerations or other more serious complications; • 9 (6%) SpaceOAR™ Hydrogel procedural rectal wall infiltration. • 2/149 spacer patients had no SpaceOAR™ Hydrogel present after application: hydrogel injected beyond the prostate in 1 patient, no hydrogel injected in the other due to inadvertent needle penetration of the rectal wall requiring study-mandated termination of the procedure.		Important 1 RCT ⨁⨁⨀⨀ LOW[2,3]	The information reported in the RCT and companions studies: Mariados 2015, Piczonca 2015, Karsh and Fisher Valuck 2017

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
Abbreviations: AE: Adverse Event; CI Confidence Interval; HR: Hazard Ratio; nRCT: Non-randomized Control Trial; RCT: Randomized Control Trial; RD: Risk difference; RR: Relative Risk; RT: Radiotherapy;

[1] Assessed according to Common Terminology Criteria for Adverse Events (CTCAE v4)
[2] Downgraded one level due to limitations in design (high risk of bias) (e.g. blinding, selective reporting)
[3] Downgraded one level due to imprecision (one or two small studies)
[4] Grade 2 is presented in Mariados' publication as '>2' and in Hamstra's as '≥2'; we have assumed this is ≥2 and reported as such
[5] Downgraded one level due to limitations in design (large loss to follow-up without imputations)
[6] Downgraded one level due to limitations in design (high risk of bias) (e.g. bias due to confounding, selection of participants, bias of measurement of outcome)

Discussion

External beam radiotherapy has evolved to give the radiation oncologist the ability to treat patients faster and with higher radiation protocols. However, this increases the risk of exposing healthy tissue to radiation and producing adverse events in adjacent areas. Biodegradable spacers are a health technology that has elicited interest among clinicians and patients who wish to reduce the side effects of radiation to the rectum during the process of treating prostate cancer with radiotherapy. When oncologists insert fiducial or gold seeds perinealy for optimal radiation delivery, the spacer insertion can be done at the same time.

The use of biodegradable rectum spacers to reduce toxicity to the rectum for individuals with prostate cancer represents an emerging field. Our extensive literature search yielded two prospectively conducted studies with a comparator (one RCT and one nRCT) which included participants with localized cancer to the prostate T1 and T2 stage [4]. Low to very low-quality evidence from two small studies showed that spacers (SpaceOAR™ or balloon) may lead to little or no difference in acute or late rectal and urinary toxicity (15 months). However, at long term follow-up (median of 3 years), SpaceOAR™+RT may slightly reduce rectal toxicity. These results may differ if the selection of patients has a different baseline risk, a different RT technique is used, or patients have a higher volume prostate. Other reasons explaining why the studies, especially the RCT, may have not shown results in rectal toxicity, might be that the study was underpowered for detecting differences in relatively rare adverse event rates or might be potentially biased among those lost to longer term follow-up.

Radiotherapy with curative intent risks damaging bowel, urinary and sexual functioning which have clear consequences for patient QoL. Given the significantly improved survival for localized prostate cancer, the long-term effects on health-related patient-reported quality of life outcomes are important to consider for policy development. The literature suggests that every 8 to 10-Gy increase in radiation dose to the prostate doubles the odds of severe late-onset toxicities. SpaceOAR™ +RT was associated with benefits in bowel quality of life over the study period (p=0.002), but SpaceOAR™ +RT may lead to no difference in urinary or sexual QoL when compared to the RT group. The paucity of data severely constrains our ability to compare findings with those of other studies. The radiation protocol in this RCT conformed with guidelines, but how results in bowel, urinary and sexual QoL compare to current RT techniques is unclear.

Evidence from 1 RCT and 1 nRCT showed a reduction in the amount of radiation to the rectum with the use of SpaceOAR™, gel and balloon when added to RT. However, given results for toxicity presented previously, we are unclear how that reduction in rectal dose translates into clinical benefits for the patients. PSA values were similar at 12 and 15 months follow-up between intervention and RT groups [11] and, surprisingly, the authors did not report PSA at 36 months. The distance between the rectum and the prostate increased after insertion; but it is worth remembering that the men in the studies had T1 and T2 stage diagnosis. The creation of an effective perirectal space as well as the potential to disseminate tumour cells within the pelvis in locally advanced prostate cancer needs consideration. Also, it is important to consider the above outcomes are not clinical outcomes (computed by the planning system) and must be considered as surrogates.

In light of uncertainties surrounding currently available evidence, it is unclear whether the costs and expertise involved in carrying out this (invasive) type of intervention warrant its general use in any men with localized T1 or T2 stage prostate cancer.

The studies included had limitations; the RCT was weakened by the possibility of unblinding patient assignment, selective reporting, as well as high attrition during long-term follow-up. One concern is whether outcomes measured over the long term can be attributed to SpaceOAR™. Loss to follow-up in the RCT (>20%) is considered large, which weakens the validity of the results. Authors should anticipate loss to follow-up (or death) in the planning phase for the long-term follow-up (36 months) and design the trial in a way that facilitates analysis (in respect of predictable data collection for conducting appropriate statistical analysis). We were unable to find information for the planning of the long-term follow-up in the ClinicalTrial.gov trial registry record.

The nRCT limitations related to confounding and selection bias in that the study had a very small sample and short follow-up period. Another limitation of this study was that the individuals in the control group had severe co-morbidities and compulsory anticoagulation, indicating perhaps a different patient group to those who received the intervention of interest (gel or balloon).

Conclusion

Given the small number of trials, small sample sizes, and narrow inclusion criteria reported in the published research, along with the low to very low certainty of evidence, it is difficult to comment on benefits and harms of biodegradable rectum spacers (SpaceOAR™ or balloon). Future research will likely change our understanding of this intervention.

A larger body of knowledge is needed to guide practice. Future research may need to broaden its remit to other RT techniques, doses and cancer stages. This may help to confirm and expand our results. Although previous Health Technology Assessments (HTAs) have suggested the need for RCTs, our search found a large number of posters, abstracts, and single-arm studies on the technologies of interest. Single-arm studies could provide further information on adverse events, but are of limited value for proving the effectiveness of the technology.

1 SCOPE

1.1 Description

Description	Project Scope
Population	Adults (>18yrs) who have a prostate cancer diagnosis and receive radiotherapy with curative intent, meaning radical doses of radiotherapy, either for first-time or recurrent cancer. Within this assessment, we included cancers confined to the prostate gland (vs cancers with extracapsular growth and/or infiltrating seminal vesicles) of both non-metastatic and metastatic types. The latter means where the cancer has spread from the main tumours to other areas of the body. We included adenocarcinomas and any other types of prostate cancer requiring radiotherapy. We included individuals undergoing curative treatment radiotherapy alone or alongside hormone therapy (e.g. androgen deprivation therapy). Exclusion criteria: Individuals undergoing palliative treatment, since the radiation dose (and therefore toxicity to the rectum) may differ from those receiving radiotherapy for curative purposes. Individuals in a postoperative stage. The placement of prostate fiducial marker seeds was not considered a postoperative stage in this assessment. Intended use of the technology: Specialist health care ICD 10 codes: Malignant neoplasm of prostate C61, C79.82, Z79.81, C79.49, Z85.46, R97.21, D07.5 ICD 10 codes: Radiotherapy Z51.89, D01, D71. D81, D91, DB1, DD1, DF1, DG1, DM1, DT1, DU1, DV1, DW1 Mesh-terms: prostatic neoplasms;
Intervention	Because the anterior wall of the rectum is positioned behind the prostate, it is vulnerable and at risk of radiotherapy adverse effects. Sparing the anterior rectal wall is an important priority. Rectum spacers may help here; spacers are inserted in the body temporarily to increase the separation between the prostate and the rectum. The main purpose is to decrease the damage caused to the rectum during radiotherapy which may be due to the close proximity of the prostate to the rectum. This assessment included CE-marked technologies that have an approved indication: - SpaceOAR™, manufactured by Boston Scientific. Material: Synthetic PEG-based hydrogel - ProSpace System (rectal balloon) by BioProtect. Material: bioresorbable polymer - Barrigel™ manufactured by Palette Life Sciences Material: stabilized sodium hyaluronate also named Non-Animal Stabilized Hyaluronic Acid (NASHA) The above technologies were assessed when used in combination with one or more of the following: a. Radiation therapy (or radiotherapy) is an established treatment used to slow the progression or cure the disease. External-beam radiotherapy (EBRT) from outside the body from a radiotherapy machine or brachytherapy (also called internal or

	interstitial radiotherapy) are common forms of radiation. Brachytherapy can be given at either a low dose rate (LDR) or a high dose rate (HDR). LDR or HDR brachytherapy may be used alone or in combination with EBRT. Intensity-modulated radiotherapy (IMRT) is a type of EBRT that uses CT scans to form a 3D picture of the prostate before treatment and uses this information to determine how much radiation is needed. Proton (beam) therapy uses protons rather than X-rays. If studies included older techniques (e.g. 3D conformal), these were included, with the acknowledgement that they might produce higher rectal toxicity and a benefit for spacers that cannot be transferred to modern techniques. Fractionation: using fraction sizes >2Gy per day may be radio-biologically advantageous. There is evidence that doses beyond 80Gy can be delivered safely with image-guided intensity-modulated radiotherapy (IG-IMRT). HDR brachytherapy is an alternative means of delivering hypofractionated radiation as a boost to achieve dose escalation after 45-46Gy in 1.8-2Gy daily fractions or 37.5Gy in 15 fractions. b. Hormone therapy (lowering androgens levels) is often used in combination with radiotherapy to either increase the chance of successful treatment or reduce the chances of recurrence. It can be given before, during and after radiotherapy to increase overall treatment effectiveness. c. Chemotherapy Intended Use: Therapeutic MeSH terms: Hydrogels/pd [pharmacology]; Hydrogel, Polyethylene Glycol Dimethacrylate/administration & dosage; hyaluronic acid
Comparator	Management pathway without the technology (e.g. radiotherapy)
Outcomes	The assessment team's consensus was that (acute or late) rectal toxicity was the main endpoint. Additional outcomes of interest in this report are overall quality of life and any sub-endpoints (e.g. sexual, urinary or bowel quality of life), overall survival, urinary toxicity, reduction in rectal radiation dose, increased distance between prostate and rectum, prostate-specific antigen (PSA) and adverse events (acute and late) that are device related. **Main endpoint** Toxicity **Secondary endpoints** Overall QoL and any sub-endpoints relating to it (e.g. sexual or bowel QoL) Overall survival, Urinary toxicity Reduction in rectal radiation dose Increase distance between prostate and rectum PSA relapse Adverse events We included outcomes measured at short and long follow-up times, i.e. measured within one year, one to three years, more than three years after the intervention. For safety data, we included adverse events being attributed to rectum spacers, as well as radiotherapy, or hormone therapy or their combinations, since interactions are possible and assumptions about the actual biological pathways are not always correct. The selection of outcomes was informed by the COMET initiative resources on core outcomes for prostate cancer [14], the James Lind Alliance [15] 10 top

	priorities for research, and ultimately by consensus reached by the OTCA23 assessment team (dedicated reviewers, co-authors, clinical expert and patient partner involved) with the aid of patient input from Prostate Cancer UK. For adverse events, the James Lind Alliance research priorities specify an interest in short-term side effects, long-term side effects (those which last for years after treatment) and late side effects (those which do not appear until years after treatment).
Study design	**Effectiveness:** Inclusion criteria: Randomized controlled trials and non-randomized controlled trials or observational studies with a control group. In this assessment, nRCTs are experimental studies in which participants are allocated (prospectively) to different interventions using non-random methods. Prospective studies or registry studies, defined as studies that sample patients with both a specific outcome and a specific exposure, or that sample patients with a specific outcome and include patients regardless of whether they have specific exposures; and which do not permit calculation of an absolute risk [16]. Exclusion criteria: Studies with designs different from the above (e.g. retrospective or historical design) based on data retrieved from sources other than registries (e.g. chart reviews, electronic health records, patient surveys, case reports). **Safety:** Inclusion criteria: Randomized controlled trials, non-randomized controlled trials or observational studies. Exclusion criteria: Studies with designs different from the above based on data retrieved from sources other than registries (e.g. chart reviews, electronic health records, patient surveys) We screened the literature to identify any publications on MIDs for the outcomes included in this assessment. We rated the importance of each outcome for decision making as described in Table 1.1
Language	We did not apply language restrictions.

1.2 Rating of the importance of outcomes for decision making

In accordance with the GRADE approach, we graded the importance of each outcome through a structured process. Each outcome was rated as critical (score 9-7), important but not critical (score 6-4) or of low importance for decision-making (3-1) [17]. If participants felt that they did not have enough information to make a judgement, they were invited to answer with “do not know”. (See Table 1-1)

We collected the ratings from the clinical experts, and the members of the assessment team. The team’s patient partner and the patient organization which provided input at the scoping phase

were invited to rate the outcomes. While the clinical experts took a clinician's perspective, the assessment team took a policy-maker's perspective, and patients provided patients' perspectives.

We used online survey software to collect the individual votes. We performed the prioritisation of outcomes in the late phase of the assessment.

Table 1-1: Rating of the importance of outcomes

EFFECTIVENESS	Ratings	Final rating		
	Assessment team (n=4) Patients (n=0) Clinical experts (n=2) (median and min-max)	Critical	Important	Not important
Rectal Toxicity	8.5 (8-9)	●	○	○
Overall QoL	7.5 (6-9)	●	○	○
Sexual QoL	5 (5-6)	○	●	○
Bowel QoL	6 (6-8)	○	●	○
Overall survival	4 (1-9)	○	●	○
Urinary toxicity	7 (3-9)	●	○	○
Reduction in rectal radiation dose	6.5 (0-8)	○	●	○
Increase distance between rectum and prostate	6 (3-6)	○	●	○
PSA Relapse	4 (1-6)	○	●	○
SAFETY	**Ratings**	**Final rating**		
	Assessment team (n=4) Patients (n=0) Clinical experts (n=2) (median and min-max)	**Critical**	**Important**	**Not important**
Mild to moderate AE (grades 1 to 2)	6 (4-6)	○	●	○
Severe to life-threatening AE (grades 3 to 4)	9 (8-9)	●	○	○
Death related to AE (grade 5)	9 (5-9)	●	○	○

AE = adverse events; QoL= Quality of Life; PSA = prostate-specific antigen

Appendix 3 - Table A12 provides an overview of the individual ratings per outcome.

2 METHODS AND EVIDENCE INCLUDED

2.1 Assessment Team

The assessment team organized the tasks as described below:

NIPHNO (author)

- Overall responsibility for production and quality of the assessment
- Recruited clinical experts, patient partners and patient organizations
- Performed the scoping and literature search
- Collected the DOICUs from everyone involved in the assessment
- Developed the first draft of the project plan
- Carried out the assessment: selected and answered assessment elements (for the EFF and SAF domains)
- Coordinated the GRADE process for rating the importance of outcomes for decision-making
- Filled in the checklist of potential “ethical, organizational, patient and social and legal aspects” of the HTA Core Model for rapid REA
- Quality-checked the production process for the TEC and CUR domains
- Sent draft versions to reviewers (dedicated reviewers, clinical experts, manufacturers, patient organization) for comments, compiled feedback from reviewers and incorporated relevant changes to the draft
- Prepared all draft versions and the final assessment including an executive summary

NSPHMPDB (co-author)

- Reviewed the project plan draft
- Selected and answered assessment elements for the TEC and CUR domains
- Contributed to rating the importance of outcomes for decision making
- Supported the production of the assessment report
- Contributed to answering questions related to potential ethical, organizational, patient and social and legal aspects if needed
- Approved/endorsed conclusions drawn

Dedicated reviewers (SNHTA, VASPVT, NICE, IQWIG)

- Thoroughly reviewed draft project plan and drafts report including studies and results
- Contributed to rating the importance of outcomes for decision making
- IQWIG, dedicated reviewer specifically for information retrieval content only

The clinical experts supported the assessment team by:

- Discussing the project scope with the assessment team
- Reviewing the project plan
- Rating the importance of outcomes for decision-making
- Providing expert advice on the interpretation of study findings
- Reviewing the draft assessment

2.2 Source of assessment elements

We used the HTA Core Model Application for rapid REA (4.2) to select assessment elements. For each selected assessment element, we then formulated a specific research question.

2.3 Search

We used the HTA reports by the Canadian Agency for Drugs and Technologies in Health (CADTH), Cancer Care Ontario (CCO) and NICE [18-20] as a starting point for this assessment. These reports were identified through a scoping search by an information specialist at NIPHNO. The above assessments were published in February 2019, January 2019 and 2017 respectively;

however, none had the same PICO/scope as this assessment. While CADTH and CCO focused on hydrogel only, NICE's report was an overview including all types of study designs.

The search strategy for this assessment was developed by an information specialist at NIPHNO and critically appraised by an information specialist at Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). The search strategy was based on the population and the intervention in the PICO. It contained both index terms and text words to identify as many relevant studies as possible. The actual information retrieval process was performed by the NIPHNO information specialist.

As a first step, we looked for relevant systematic reviews and HTAs (i.e. search I) to prevent duplication of efforts. The use of findings of existing evidence syntheses could include use of the results of existing searches and/or use of data extraction, study-level risk of bias assessments or synthesis [21]. In order to include a synthesis in this assessment, the scope of existing evidence syntheses had to match the scope of this new assessment. Further, we planned for two reviewers to independently appraise the methodological rigour of any relevant review with the AMSTAR II instrument [22]. In a second instance (i.e. search II), we looked for primary studies.

The references' titles, abstracts and full texts were screened by two people independently. Reference lists of relevant systematic reviews and included studies were screened accordingly. In addition, we asked manufacturers of rectum spacer devices to inform us about any published and unpublished (but not confidential) clinical studies/clinical data concerning their products.

Appendix 1 includes the detailed search strategy. We did not apply language, design or publication status restrictions. The searches were executed on 11,12 and 18 November 2019 with a year limit of 2010-2019 in the following databases:

Search I: Systematic Reviews and HTA:

Cochrane Library: CDSR Reviews
Cochrane Library: Trials (CENTRAL)
Centre for Reviews and Dissemination (NIHR) – HTA
MEDLINE
Embase
Epistemonikos
National Guideline Clearinghouse
Guidelines International Network (GIN)
HTAi Vortal (HTAi: Health Technology Assessment International). Hand search CADTH, NICE, NIHR, AETSA, AHRQ, SBU
Devices@FDA

Trial registry record regarding status
Clinical Trials (US)
ICTRP (WHO)
PROSPERO
POP Database

Search II: Primary Studies

- Cochrane Library: Trials (CENTRAL)
- MEDLINE
- Embase
- Epistemonikos
- Devices@FDA

Trial registry record regarding status

- Clinical Trials(US)
- ICTRP (WHO)
- American Society of Clinical Oncology conference abstracts
  Radiation Therapy Oncology Group (RTOG) clinical trials protocols

For the TEC and CUR domains, we considered the information from the three reports mentioned previously [18-20] in addition to information coming from current clinical practice guidelines, information from a general literature search, the input from clinical experts and information collected through web searches. The manufacturers were invited to complete the EUnetHTA submission file for the chapters: 1. Description and technical characteristics of the technology, 2. Health problem and current clinical practice, 3. Current use of the technology, 4. Investments and tools required.

2.4 Study selection

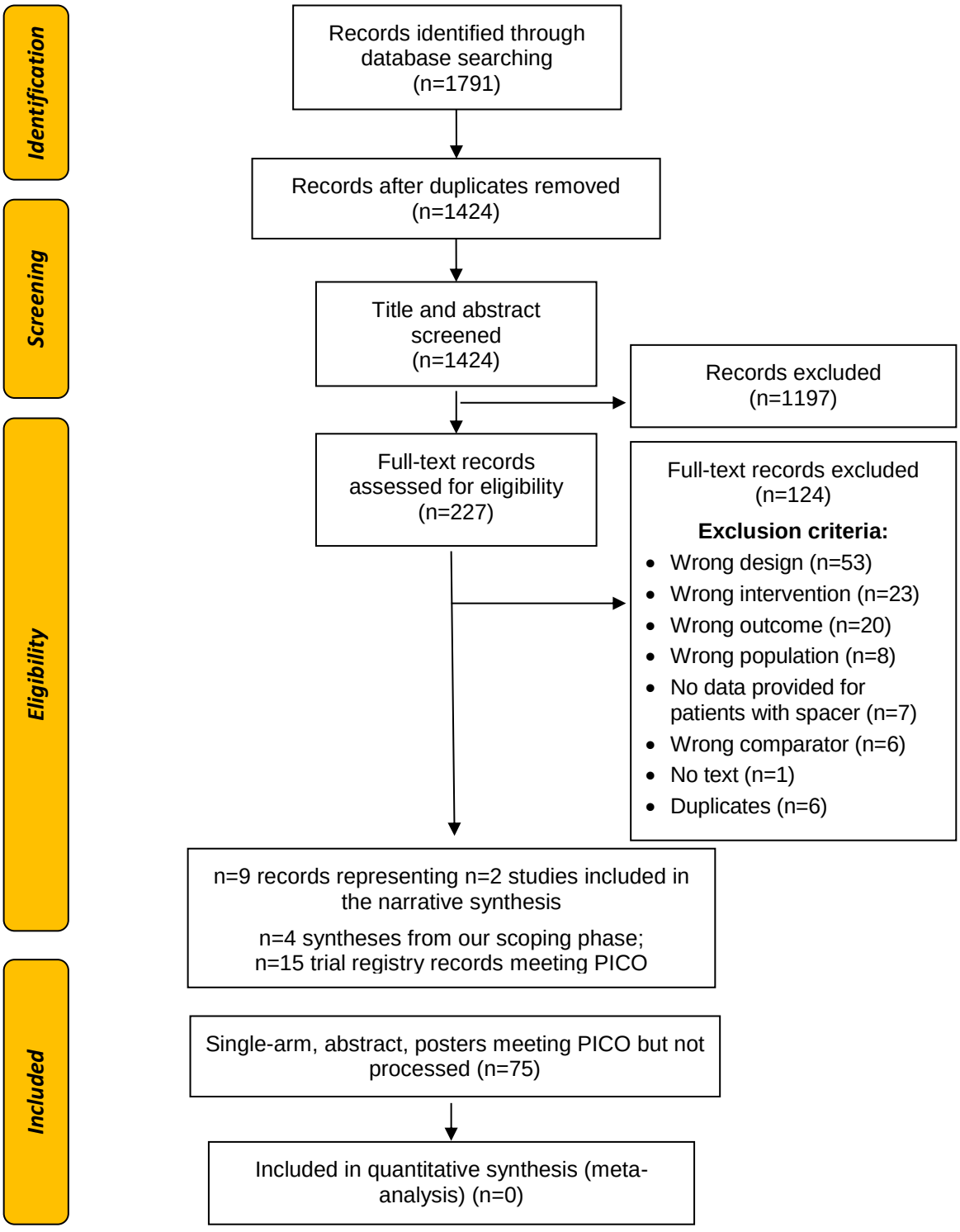


Figure 1: Flow chart

The search for systematic reviews, HTAs and guidelines yielded 4 results (including those found at scoping phase) and the search for primary studies provided 1791 records. The screening of reference lists from included studies resulted in zero additional references and the manufacturers informed us about studies captured by the search and an additional systematic review towards the end of the assessment [23]. After removal of duplicates, we ended up with 1424 references. Two reviewers independently screened studies retrieved through the literature search against the predefined inclusion and exclusion criteria. After screening of titles and abstracts, we excluded

1197 references. In the next step, we screened the remaining 227 studies in full text. There was a small number of prospective studies with a comparator (RCTs or nRCTs). More detailed information is given in Appendix 1 Tables A1 and A2

Our protocol inclusion criteria for safety stated inclusion of "RCTs, nRCTs or observational studies, single-arm trials and single- or multiple-arm prospective registry-based data." We included 2 unique studies for analysis as explained in Table 2.1 study pool below. In addition, we included 15 trial registry records (see Table 2-2) meeting our PICO. Appendix 1 Table A3 reports the PICO characteristics of trial registry records in more detail. As well, the single-arm, abstract and poster records (n=75) met our PICO. However, given the high number of records we found, we were unable to follow up with trialists to find out if posters and abstracts had available results or full-text publication (Appendix 1 Table A4). As most of these posters and abstracts were from single-arm studies, the team placed all single-arm, poster and abstracts results in an appendix for future evaluation.

For the two included studies, if there were preliminary results, end-of-intervention and follow up-results, we used the final and follow-up results only. The study selection process was double-checked by the co-author team.

Table 2-1: Study pool – list of studies included in the assessment

Study Reference/ID	Available documents (i.e. companion studies)	Study registry entries (Reference)/Result report from study registries
Mariados 2015 [4]	Pieczonka 2015 [24] – Abstract Pieczonka 2015 [7] – Full text Fischer-Valuck 2017 [25], Full text, no comparative data Karsh 2017 [12] – Review Hamstra 2017 [26] – Abstract Hamstra 2017 [6] – Full text Hamstra 2018 [5] – Full text	NCT01538628 [8], no results reported
Wolf 2015 [9]	--	--
Synthesis from Scoping Phase		
NICE [20] Chao 2019 (CADTH) [18] Chung 2019 [19] Forero 2018 [27]	--	--

Table 2-2: Trial registry record pool

Trial Registry Number	Status	Study Design	Intervention/control
NCT02353832 [28]	Active, not recruiting	Single arm	Hydrogel
NCT03663218 [29]	Active, not recruiting	Single arm	Unclear
NCT00918229 [30]	Completed	Single arm	BioProtect – Balloon
NCT01538628 [8]	Completed	RCT	Hydrogel vs control
NCT02212548 [31]	Completed	Single arm	Hydrogel
UMIN000026213 [32]	No longer recruiting	Single arm	Hydrogel
UMIN000038131 [33]	No longer recruiting	Single arm	Hydrogel

ACTRN1261000524897 [34]	Not yet recruiting	Single arm	Hydrogel
NCT03400150 [35]	Recruiting	RCT	Balloon vs control
NCT03525262 [36]	Recruiting	RCT	Hydrogel
NCT03386045 [37]	Recruiting	RCT	Hydrogel
NCT02478112 [38]	Suspended	Single arm	Balloon
NCT01999660 or DRKS 00006409 [39]	Unknown	Case control	Hydrogel vs unclear
NCT02165020 [40]	Unknown	nRCT	Hyaluronic acid vs unclear
NCT02361515 [41]	Unknown	RCT	Hyaluronic acid vs unclear

2.5 Data extraction and analyses

One reviewer used an online pre-piloted form to extract data from the studies, with a detailed review by another reviewer. For a few trial registry records, we contacted the main investigator(s) to inquire about the availability of a full-text publication (information recorded in Appendix 3 Table A13).

We extracted the following data from the included studies:

- Study details: author's name, year of publication, trial protocol identification number, sponsorship source, country, setting, language, declaration of interest, contact with authors
- Methods: study design, type of analysis (e.g. per protocol, intention to treat), characteristics of trial design as outlined in the assessment of risk of bias
- Population: inclusion criteria, exclusion criteria, total number and number per group, baseline characteristics (age, tumour characteristics, comorbidities). Tumour characteristics include: disease status (primary, recurrent, prior surgery), tumour size, tumour grading, tumour stage
- Intervention and comparator characteristics: description of procedure and comparators and concomitant treatments. For radiotherapy, we extracted data about type of radiation, dose, number of fractions, and total treatment time
- Outcome: primary/secondary endpoints as specified in the PICO table above, type, effect measure, scale, number lost to follow-up, follow-up period, treatment discontinuation with reason

We included one RCT (containing 8 additional records) and one nRCT. We planned that if two or more (RCT or nRCT/observational) studies reported on the same outcome, we would perform meta-analysis using techniques as described in the Cochrane Handbook [42]. However, the evidence available on the different spacers varied significantly, so we present the clinical evidence separately, with the aim of minimizing the risk of erroneous conclusions. We calculated effect sizes for urinary and rectal toxicity (short and late) and QoL (with data provided by the manufacture); in all other instances we present data as reported in the individual studies.

Toxicity outcomes (urinary and rectal) and adverse events are reported in accordance with CTCAE v4 [10]. We reported acute or late toxicity as mentioned in the included studies.

To interpret the magnitude of effect sizes, we screened the literature to identify accepted standards for MIDs for the outcomes that we selected in this assessment. Within this context, we referred to Minimally Important Difference for the Expanded Prostate Cancer Index Composite Short Form [43]. Table 2-3 below presents the recommended EPIC MID values.

Table 2-3: Minimally Important Difference recommended values

EPIC Domain	Recommended Value
Urinary Incontinence Urinary irritative/obstructive Bowel Sexual Vitality/hormonal	6-9 points 5-7 points 4-6 points 10-12 points 4-6 points

2.6 Quality rating

Two reviewers independently appraised the risk of bias at study level with the Cochrane Risk of bias tool [1] and the ROBINS-I tool [2]. Any disagreements were resolved by discussion. We had no restrictions for inclusion in respect of the risk of bias.

For both designs, if an individual domain had a high/serious risk, the overall judgement of the risk of bias was that the study as a whole had a risk of bias at least this severe. Therefore, a judgement of “high” risk in any domain had similar implications for the study as a whole, irrespective of which domain was being assessed.

We planned to perform sensitivity analyses according to the different risk of bias categories, but omitted this because meta-analysis was not applicable.

To rate the certainty of the evidence for each outcome, we used GRADE. For each outcome, we took into account the risk of bias, imprecision, inconsistency, indirectness and publication bias. We expressed certainty as high, moderate, low or very low as defined by the GRADE working group [3, 17].

For the TEC and CUR domains, no quality tool was used. Clinical experts and manufacturers reviewed the descriptions provided below.

2.7 Patient involvement

We invited patients and patient groups in each team country (i.e. Norway, Romania, Switzerland and the United Kingdom) and extended the invitation to participate in the OTCA23 assessment through EUnetHTA social media. The published open call for patient involvement on the EUnetHTA website was combined with an invitation to European umbrella organizations.

We included a patient partner as part of the team and received input from a patient organization (i.e. Scotland Prostate). The patient organization was recruited following an English HTA organization inquiry to the EUnetHTA secretariat about the assessment during the scoping phase. The aim of patient involvement and input at the scoping phase was to capture their experiences with -and -views- of the disease, the intervention being assessed, and outcomes of interest. Both patient partner and organization were invited to provide feedback and input at scoping/protocol writing phase, importance outcome rating step, and final report stage.

2.8 Description of the evidence used

Table 2-4: Main characteristics of studies included

Author and year or study name	Study type	Number of patients	Interventions vs Comparator	Main endpoints	Included in clinical effectiveness and/ or safety domain
Mariados 2015, Pieczonka 2015, Hamstra 2017, Hamstra 2018, Fischer-Valuck 2017 Karsh 2017	RCT	220	SpaceOAR™ +RT vs RT alone	- Proportion of patients achieving >25% reduction in rectal volume receiving at least 70 Gy (rV70) due to spacer placement - Proportion of patients experiencing grade 1 or greater rectal or procedural adverse events (AEs) in the first 6 months - Rectal and urinary toxicity - Bowel,urinary and sexual QoL - PSA - Rectal dose - Increased distance volume	EFF SAF
Wolf 2015	nRCT	78+18	Gel or balloon+RT vs RT alone	- Spacer volume reduction between groups (based on dose surface histogram) - Rectal dose - Spacer stability - Balloon spacer volume - Rectal toxicity	EFF

Abbreviations: EFF= effectiveness, SAF= safety

2.9 Deviations from project plan

- The number of single-arm studies, either as abstracts, posters, or full text was much greater than expected. We have placed single-arm studies or studies with a comparator that were abstracts or posters in Appendix 1 Table A4. The team acknowledges that the conduct of RCTs may present difficulties and these studies may provide further information on safety, efficacy and emerging technologies (e.g. BioProtect Balloon, HA).

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

3.1 Research questions

Element ID	Research question
[B0001]	What are the technologies and the comparator(s)?
[A0020]	For which indications have different types of rectum spacers devices received marketing authorisation or CE marking?
[B0002]	What is the claimed benefit of rectum spacers in relation to the comparators?
[B0004]	Who administers rectum spacers and the comparators and in what context and level of care are they provided?
[E0001]	What types of resources are deployed when using the different types of rectum spacers?
[A0021]	What is the reimbursement status of rectum spacers in the different EU countries?

3.2 Results

Features of the technologies and comparators

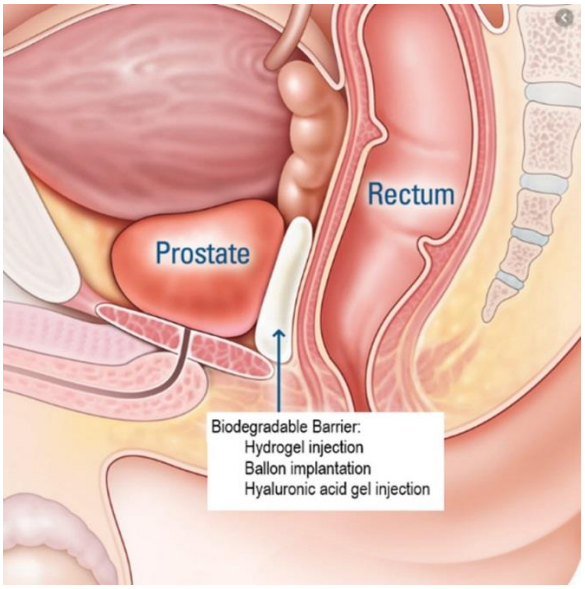
[B0001] – What is a biodegradable rectum spacer and what is prostate cancer radiotherapy?

Biodegradable Rectum Spacers for Prostate Cancer Radiotherapy

The technologies under assessment are biodegradable rectum spacers, used to reduce toxicity during prostate curative radiotherapy. A main treatment option for prostate cancer (with surgery being second) is radiotherapy, which has a number of proven benefits and high efficacy for certain types and stages of prostate cancer; however, the necessary dosage and therapeutic schemes as well as the zonal anatomical conformity and proximity to the rectum present a risk of damage to the surrounding organs and tissues. Due to the proximity of the prostate and the rectum (the rectum anterior wall is positioned in front of the prostate), the rectum is one of the main organs susceptible to damage during radiotherapy. Side effects produced by radiotherapy include diarrhoea, incontinence, proctitis and ulceration of the rectal mucosa [20].

Dose escalation can limit cancer recurrence and improve overall treatment success. Progress in the field of prostate cancer treatment highlights the efficacy of the novel radiotherapy modalities such as hypofractionation in reducing the number of daily fractions (from over 40 to fewer than 20), while increasing the daily dose. Since prostate cancer is highly sensitive to fraction size, hypofractionation could become the standard of care for localized prostate cancer, making EBRT a more cost-effective and attractive treatment modality, with a profound impact on patient quality of life. However, an increase in daily dose could cause even more extensive damage to surrounding healthy tissue (notably the rectum) [44]. In this context, reducing rectum damage by radiotoxicity is a therapeutic priority [20]. A feasible solution consists of an interposition between the two organs (prostate and rectum) as a barrier against the penetration of radiation into the rectum and tissues during radiotherapy period (Figure 3-1).

Figure 3-1: Rectum spacer diagram



Source: Adaptation after SpaceOAR™ Hydrogel diagram (with permission), available at: https://www.premiermedicalhv.com/wp-content/uploads/2018/05/LateralwProduct-Callouts.jpg

Current medical devices used during prostate cancer radiotherapy bear the generic name of biodegradable rectum spacers. The main mechanism by which biodegradable spacers reduce the adverse effects of radiotherapy is to temporarily increase the distance between prostate and rectum so as to decrease the penetrative power of radiation to the rectum during radiotherapy. In prostate cancer, a number of biodegradable materials have been tried and evaluated for use as rectum spacers, including biodegradable substances such as polyethylene glycol (PEG) hydrogels, HA, collagen, or saline-filled balloons. The procedure involves injecting the biodegradable substance in the space between the rectum and the prostate. The procedure is short (~15min) 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 [19]. Estimates suggest the substances take approximately three months to liquefy by hydrolysis and absorb and clear the body by renal filtration [7].

Table 3-1: Features of the intervention

	SpaceOAR™ Hydrogel System	The ProSpace™ Balloon System	Barrigel™
Product code/Model	SO-1010/ SpaceOAR™ System for prostate cancer applications (Class III)	BioProtect/ProSpace Balloon System	Barrigel™
Manufacturer	The manufacturer, Augmenix Inc, was acquired by Boston Scientific in October 2018	BioProtect	Palette Life Sciences
Headquarter	United States, Boston Scientific	©2017 BIOPROTECT LTD., Israel	Santa Barbara, California
Names	SpaceOAR™ / SpaceOAR™ Hydrogel/ SpaceOAR™ Hydrogel System	BioProtect/ProSpace Balloon System	Barrigel™
WEB Page	https://www.bostonscientific.com/en-US/Home.html	https://bioprotect.com/	https://www.palettelifesciences.com/barrigel

Note: products were identified using a web-based search. The list of these devices is not exhaustive.

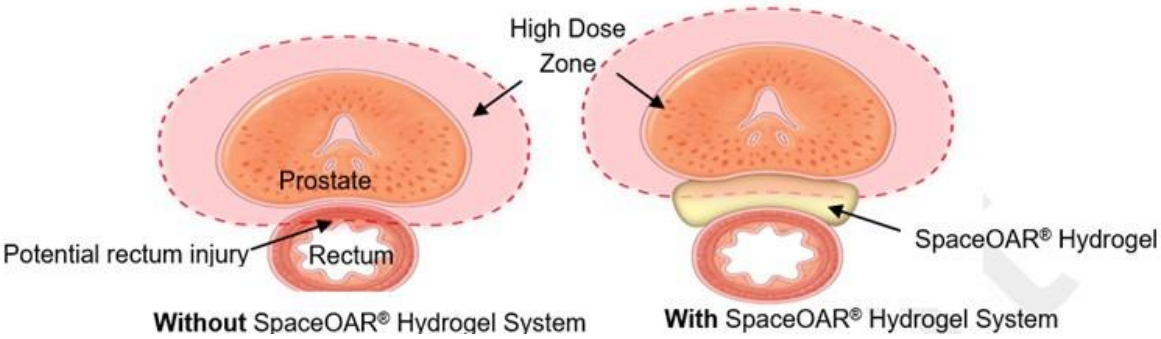
Table 3-2: Biodegradable Rectum Spacers regulatory status

	Biodegradable Rectum Spacers		
Model	Hydrogel: SpaceOAR™ System for prostate cancer applications (Class III)	Balloon: The ProSpace™ Balloon System	Gel: Barrigel™
Manufacturer	The manufacturer, Augmenix Inc, was acquired by Boston Scientific in October 2018, United States	BioProtect, Israel	Palette Life Sciences, Sta Barbara, CA
CE mark	Yes	Yes	Yes
Date of approval	10 March 2010	Information not found	23 January 2014
FDA approval	YES	Undergoing clinical studies prior to FDA regulatory approval	Undergoing clinical investigation prior to FDA approval
Date of approval	April 2015	-	--
Other regulatory approvals	Australia (Therapeutic Goods Administration; Jan. 2011) Canada (Health Canada; Feb. 2016) Japan (Pharmaceutical and Medical Devices Agency; May 2017)	-	Therapeutic Goods Administration Clearance (Australia); date of Approval: 3 of July 2020
Intended use	Hydrogel Polymers and Associated Accessories to be used as Spacers and/or Fillers for Oncologic Radiotherapy. The purpose of SpaceOAR™ Hydrogel System is to create a space between the prostate and the rectum which reduces the amount of radiation delivered to the rectum during radiotherapy treatments.	The ProSpace™ System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent of the ProSpace System to reduce the radiation dose delivered to the anterior rectum.	Barrigel™ is used to increase the distance between the prostate and the anterior rectal wall, with the intent to decrease radiation dose delivered to the rectum when treating prostate cancer with radiation.
Range of applications	In combination with Oncologic Radiotherapy. Prostate cancer with radiotherapy.	In combination with Oncologic Radiotherapy. Prostate cancer with radiotherapy.	In combination with Oncologic Radiotherapy. Prostate cancer with radiotherapy.
Contraindications	No contraindications	No contraindications	No contraindications

*Augmenix, Waltham, MA

SpaceOAR™ Hydrogel. SpaceOAR™ Hydrogel is designed to temporarily position the anterior rectal wall away from the prostate to reduce the radiation dose delivered to the anterior rectum (radiation high dose region) during radiotherapy sessions as shown in Figure 3-2 below. The safety, efficacy, economic, and quality of life impact of SpaceOAR™ Hydrogel System has been evaluated in over 75 publications, including a prospective multi-centre RCT [4]; a 5-year comparative cohort study in 2017 [45] and numerous cohort studies conducted in the United States, the United Kingdom, Germany, Australia and other countries. The product code is SO-1010; there is only one version of the device, developed and distributed by Boston Scientific.

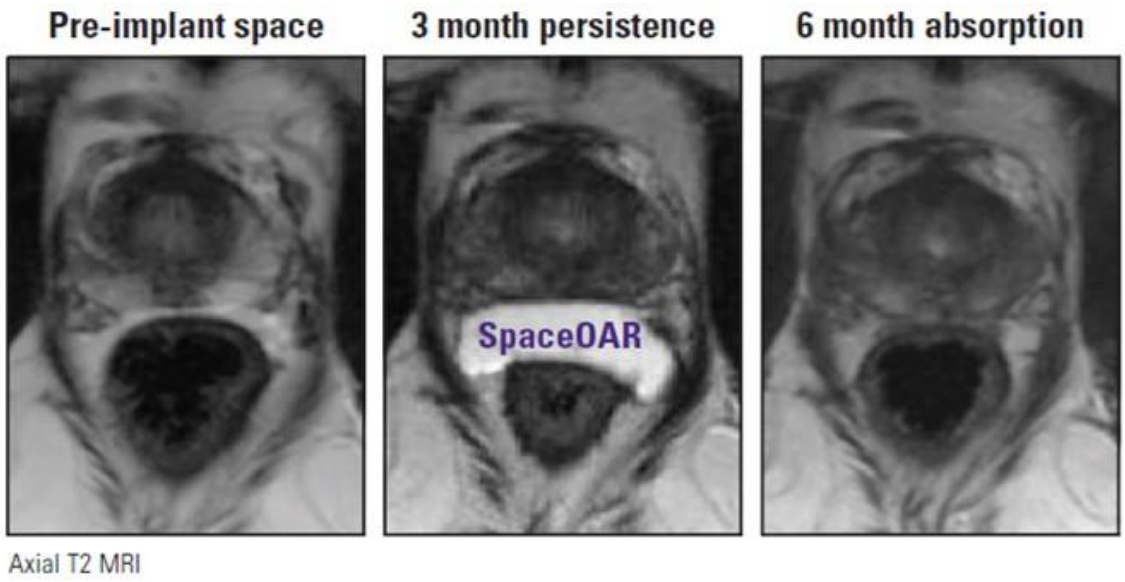
Figure 3-2: SpaceOAR™ Hydrogel pushing the rectum out of the radiation high-dose region (right) [46].



Source: image retrieved from the public domain, namely Orange County CyberKnife and Radiation Oncology Center [47]

SpaceOAR™ Hydrogel maintains a stable space for approximately 3 months allowing enough time to support the intended use (i.e. pushing the rectum away from the prostate during the complete course of radiotherapy treatment) and is absorbed into the body and cleared in the patient's urine at about 6 months as shown in Figure 3-3 below.

Figure 3-3: MRI images of the same patient at baseline (left), after SpaceOAR™ Hydrogel (middle) and 6 months after SpaceOAR™ Hydrogel (right) [4]



Source: image retrieved from the public domain, available at Orange County CyberKnife and Radiation Oncology Center website [47]

The SpaceOAR™ Hydrogel System is provided in a sterile condition and contains all necessary components for the preparation and delivery in a single use kit [48]. SpaceOAR™ Hydrogel is injected via a minimally invasive procedure (using one 18g needle) as a liquid where it solidifies into a soft, but firm, hydrogel within 10 seconds creating an average 1cm spacing [49]. The procedure itself takes on average 15-20 minutes.

Additional equipment required for the SpaceOAR™ Hydrogel procedure includes:

- A transrectal ultrasound (TRUS) with side-fire capabilities (Axial and Sagittal)
- Stepper system (either bed or floor mounted) to stabilize the TRUS probe
- Sterile drape, gloves, 10cc and/or 20cc syringe, sterile saline

- A stand-off balloon to optimize ultrasonography imaging is recommended [49]

BioProtect/ProSpace™ Balloon System [44] is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and, in creating this space, it is the intent of the ProSpace System to reduce the radiation dose delivered to the anterior rectum. ProSpace is a balloon composed of a biodegradable material that maintains that space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time. The product is commercially available in Europe, and is undergoing clinical studies in the United States prior to FDA regulatory approval. The balloons are made of a bioresorbable polymer, and can be manufactured in any shape and form. Balloons maintain their size and shape in the body during the radiation period and naturally biodegrade over the course of treatment.

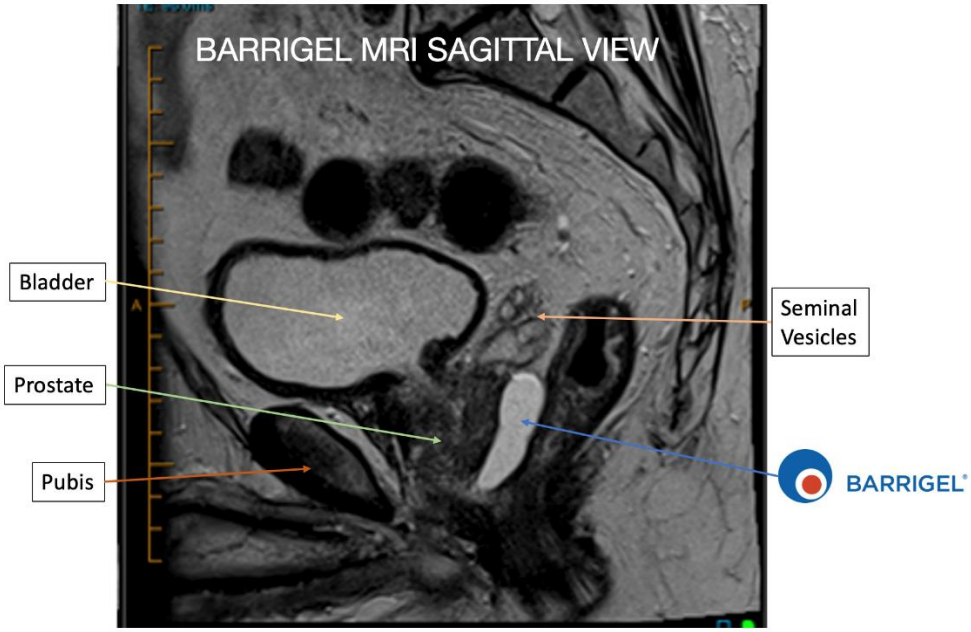
The biodegradable BioProtect Spacer is deployed in a minimally invasive procedure using a proprietary insertion device. The procedure is performed under local or general anaesthesia and guided by ultrasound. Once the balloon is *in situ*, it is inflated with sterile saline to reach the desired final configuration. The balloon implant remains inflated during the entire treatment period and completely biodegrades after six months. To assure a safe implantation of the balloon, after initial needle insertion, a blunt dissection is performed using a plastic dilator under the Denonvilliers' fascia. The blunt dissection ensures that no tissue is injured during implantation of the protective spacer [44].

Figure 3-4: BioProtect Balloon System Diagram

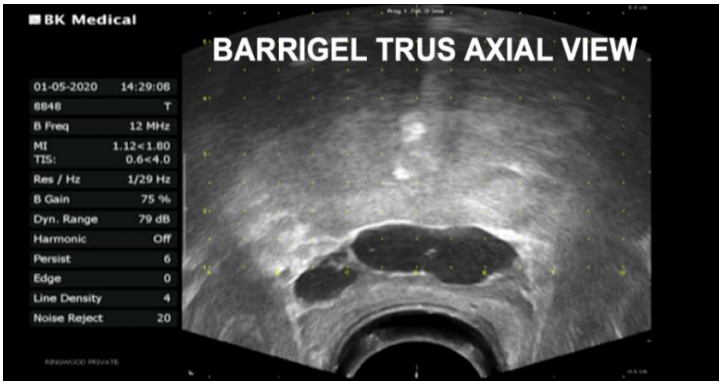
Source: image from public domain available at https://bioprotect.com/our-spacer-solution/

Barrigel™ manufactured by Palette Life Sciences [50]. A biodegradable injectable treatment for protection of the rectal wall when treating prostate cancer with radiation. The product is approved in Europe and Australia and is being investigated for market clearance in the United States. Barrigel™ is a cross-linked HA gel with a significant clinical product application in radiation oncology protecting organs at risk from radiation dose delivery. Barrigel™ uniquely allows for an image-guided trans-rectal ultrasound implant that can be sculpted to individual patient anatomy without time constraints (See Figure 3-5 below). Barrigel™ is provided as a pre-packaged, sterile, uniform gel within a syringe and requires to additional mixing or preparation prior to injection. HA is a naturally occurring glycosaminoglycan-based polymer that is naturally present in human connective tissue (in the skin and synovial fluid in the joint space) as the extracellular matrix. This compound is cleaved by the enzyme hyaluronidase to its component sub-units, which are predominantly eliminated via hepatic and renal routes. In its natural form, HA does not last very long, but HA can be modified (semi-synthesized) to remain stable for up to a year. Barrigel™ is a stable form of HA that is formed by the cross-linking of HA polymers, resulting in a scaffold with a high affinity for water. Barrigel™ is based on Galderma's proprietary Non Animal Stabilized Hyaluronic Acid (NASHA®) technology.

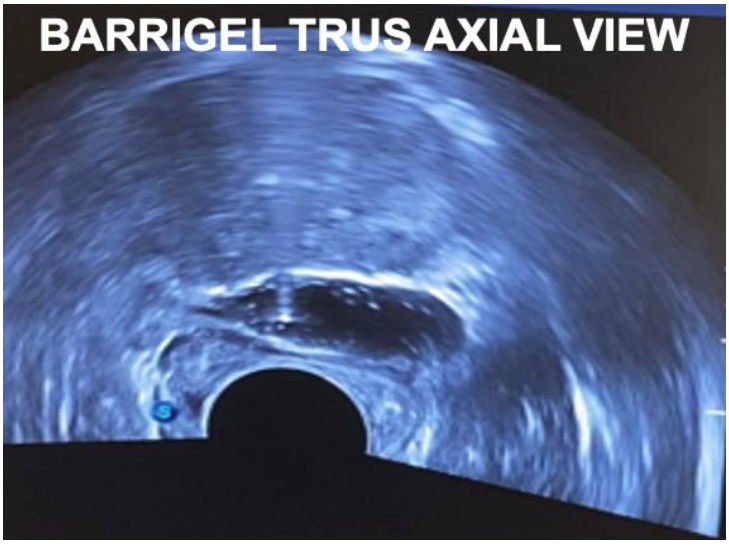
Figure 3-5: Image-guided trans-rectal ultrasound implant



Source: Palette Life Sciences



Source: Palette Life Sciences



Source: Palette Life Sciences

Prostate Cancer Radiotherapy

Radiotherapy includes several approaches using high-energy rays to destroy cancer cells; in prostate cancer, the radiotherapy used can be classified based on the location of the sources of the rays, their type and their position relative to the prostate [51], and can either be EBRT or brachytherapy.EBRT from outside the body from a radiotherapy machine and brachytherapy (also called internal or interstitial radiotherapy) are common forms of radiation. Brachytherapy can be given at either low or high dose rates. LDR or HDR brachytherapy may be used alone or in combination with EBRT [20].

IMRT, with or without image-guided radiotherapy (IGRT), is the gold standard for EBRT [52]. IMRT is a type of EBRT that uses CT scans to form a 3D picture of the prostate before treatment and uses this information to determine how much radiation is needed. Proton (beam) therapy uses protons rather than X-rays.

Fractionation: depending on the range of doses per fraction, there are two methods: conventional fractionation (1.8-2 Gy) and hypofractionation (2.5 Gy). Using fraction sizes >2 Gy per day may be radio-biologically advantageous. There is evidence that doses beyond 80Gy can be delivered safely with IG-IMRT. HDR brachytherapy is an alternative means of delivering hypofractionated radiation as a boost to achieve dose escalation after 45-46 Gy in 1.8-2 Gy daily fractions or 37.5 Gy in 15 fractions.

Recently, stereotactic body radiotherapy (SBRT) has been started to be used in the treatment of prostate cancer.

In prostate cancer, radiotherapy can also be applied in combination with other therapy (e.g. hormone* or chemotherapy) in order to slow the progression of or cure the disease:

- Hormone therapy (lowering androgens levels) in combination with radiotherapy is often used to either increase the chance of successful treatment or reduce the chances of recurrence. Hormone therapy can be given before, during and after radiotherapy to increase overall treatment effectiveness.

[B0002] – What is the claimed benefit of biodegradable rectum spacers in relation to comparators?

The main claimed benefit of rectum spacers is the protection (to the rectum) offered against the adverse effects of radiotherapy.

The EBRT effects at 6 months from treatment consist of toxicity manifested as persistent diarrhoea, bowel urgency and/or incontinence and rectal bleeding, but also an increased risk of developing secondary bladder and colorectal cancers, with similar risks over lag times of five and ten years. Absolute excess risks over ten years are small (1-4%) but should be discussed with younger men in particular [52, 53].

Brachytherapy side effects consist of significant urinary complications following implantation, such as urinary retention (1.5-22%), with post-implantation TURP reported as being required in up to 8.7% of cases, and incontinence (0-19%). Chronic urinary morbidity can occur in up to 20% of patients, depending on the severity of the symptoms before brachytherapy. Previous TURP for benign prostatic hypertrophy increases the risk of post-implantation incontinence and urinary morbidity. Prevention of morbidity depends on careful patient selection, and expert assessment of International Prostatic Symptom Score (IPSS), backed up by urodynamic studies [53].

There is some evidence on the use of spacers in the prevention of rectal toxicity to treat patients with localized prostate cancer undergoing radiotherapy. It is uncertain whether the benefits of spacers outweigh the costs and potential harms and whether spacers should be used routinely.

SpaceOAR™ System claimed benefits are:

- Reduction in rectal pain during radiotherapy;
- Reduction in rectal toxicity (diarrhoea, frequent passing of stools, rectal bleeding);

- Reduction in urinary incontinence;
- Better preservation of sexual function post radiotherapy;
- Improved quality of life in the bowel, sexual and urinary domains;
- Fewer hospital/doctor visits due to reduced bowel, urinary and sexual complications;
- Fewer therapeutic interventions to treat complications (sigmoidoscopy, argon plasma coagulation etc.);
- Additional rectal protection, to enable hypofractionated treatment regimens resulting in faster and more convenient treatment.
- Reduced readmissions because of complications of radiation therapy;
- Enabling therapy with hypofractionation regimens (reduced treatment time, fewer staff resources needed).

BioProtect/ProSpace™ Balloon System [44] has declared benefits such as**:**

- Reproducible separation: complete control over the size of the inflated implant, which is maintained throughout the treatment period;
- Safe and simple procedure: implantation under local or general anaesthesia using safer blunt dissection;
- Safe distance for dose escalation: creates a space of up to 1.8 cm, ideal conditions for dose escalation with a dramatic reduction of the risk of radiation-related complications;
- Visible under any imaging modality: the balloon boundaries are highly visible under ultrasound, CT, MRI or any other imaging modality.
- Biodegradable: within six months of implantation, no need for surgical removal.

The benefits claimed by **Barrigel™** are [50]:

- Reduces rectal toxicity from prostate radiotherapy, allowing hypofractionation regimes, improving patient outcomes and reducing healthcare utilisation
- Premixed and ready to use (no chance of mixing disasters or early polymerisation and clogging)
- Does not polymerise and therefore gives the injector the ability to sculpt the rectal spacing including the ability to achieve homogenous spacing from base to apex and from left to right.
- Controlled insertion that can be easily visualised within the perirectal space, limiting the risk of inadvertent insertion into rectum
- Barrigel™ remains stable for up to 12 months
- Barrigel™ can be reversed with hyaluronidase, a well-known enzyme on formulary at institutions

[B0004] – Who administers Biodegradable Rectum Spacer and the radiotherapy in prostate cancer and in what context and level of care is it provided?

The procedure should only be done by clinicians with training in, and experience of, transperineal interventional procedures [20]. The intended users are radiation oncologists and genitourinary oncologists involved in the management of prostate cancer. Users should be familiar with ultrasound needle placement during transperineal procedures.

SpaceOAR™ Hydrogel applications can be performed under general anaesthesia in operating room theatres but it can also be applied under local anaesthesia for day case procedures. The prerequisites imply the existence of these resources and a proper space (medical unit/specialist health care) where there is institutional support.

We found no information for ProSpace Balloon and Barrigel™ administration.

[A0020] – For which indications have the biodegradable rectum spacers received marketing authorisation or CE marking?

The CE marking of Conformity Certificate for SpaceOAR™ System in prostate cancer applications (Class III) stipulates as expected indication for Hydrogel Polymers and Associated Accessories to be used as Spacers and/or Fillers for Oncologic Radiotherapy. The CE marking conformity categorises Barrigel™ as 'stabilized non-animal hyaluronic acid-based implants for protection of the rectal wall when treating prostate cancer with radiation. CE information for BioProtect Balloon is not available beyond what is stated in Table 3-1 above.

[E0001] – What type of resources are used when employing the different types of rectum spacers?

The spacers are typically injected or inserted in a short procedure under transrectal ultrasound guidance using a transperineal approach [19]. Spacer insertion should be performed by individuals trained in the use of transperineal interventional procedures and where there is institutional support. In this sense, the spacer insertion can be performed in centres with brachytherapy services where they may choose to adapt their system to allow for the transperineal insertion of the rectal spacer within the radiotherapy 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.

The procedure is usually done with the patient under general anaesthesia. However, it may be done using local or spinal anaesthesia, depending on the planned procedures and 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 transperineal approach and transrectal ultrasound guidance. The prostate and the rectal wall are separated using saline hydrodissection. 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. With balloon spacer insertion, a small perineal incision is typically used to insert a dilator and introduce a sheath which is filled with saline and sealed with a biodegradable plug. The balloon spacer degrades over several months. Using ultrasound guidance, the dilator is advanced toward the prostate base over the needle, which is then removed [20]. For Barrigel™ the procedure consists of: uniform gel formulation (single chamber syringe, no mixing or polymerization, high lifting power and no hydrodissection required); no injection time constraints (consistent injection force, 6-10ml =1 cm + space creation, 12 months elimination); imaging on day 0 for treatment planning, due to no hydrodissection (visible on ultrasound, MRI, CT).

[A0021] – What is the reimbursement status of rectum spacers in the different European countries?

EUnetHTA partners were asked for information on the reimbursement status of rectum spacers or if an assessment was under evaluation. Partners indicated that SpaceOAR™ is currently reimbursed in Germany and Austria, there is a device specific funding for SpaceOAR™ in England via the NHS ITP programm and a device specific recommendation for reimbursement of SpaceOAR™ in France. Elsewhere an assessment has yet to be performed (see Table 3-3). Further information about device reimbursement is given in Appendix 2 Table A11.

Table 3-3: Overview of countries providing reimbursement for SpaceOAR™ Hydrogel System (Boston Scientific)

Country and issuing organization	Status of recommendation (positive/negative/ongoing/not assessed)	If positive, level of reimbursement*
Austria	Positive reimbursement through DRGs	Reimbursement not device-specific
Czech Republic	Not assessed	--
France	Device-specific recommendation	Device-specific recommendation
Germany	Positive reimbursement through DRGs	Reimbursement not device-specific
Italy	Not assessed	
Spain	Not assessed	
Sweden	Not assessed	
Switzerland	No reimbursement (decision 2014)	--
England	Device-specific funding for SpaceOAR™ via the NHS ITP programme	Full funding of device with volume cap.

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

4.1 Research questions

Element ID	Research question
[A0002]	What kind of prostate cancer is in the scope of this assessment?
[A0003]	What are the known risk factors for prostate cancer?
[A0004]	What is the natural course of prostate cancer?
[A0005]	What are the symptoms and the burden of prostate cancer for the patient?
[A0006]	What are the consequences of prostate cancer for society?
[A0024]	How is prostate cancer currently diagnosed according to published guidelines and in practice?
[A0025]	How is prostate cancer currently managed according to published guidelines and in practice?
[A0007]	What is the target population of this assessment?
[A0023]	How many people belong to the target population?
[A0011]	How much are the technologies utilized?

4.2 Results

Overview of the disease or health condition

[A0002] – What kind of prostate cancer is in the scope of this assessment?

The disease under this assessment is cancer confined to the prostate gland (vs cancers with extracapsular growth and/or infiltrating seminal vesicles) requiring radiotherapy.

Description of prostate cancer and subtypes. Prostate cancer is the second most commonly diagnosed cancer in men, with an estimated 1.3 million diagnoses worldwide in 2018, accounting for 15% of all cancers diagnosed [54]. The incidence of prostate cancer diagnosis varies widely between different geographical areas, being highest in Australia/New Zealand and North America (age-standardised rates per 100,000 of 111.6 and 97.2, respectively), and in Western and Northern Europe (age-standardised rates of 94.9 and 85, respectively), largely due to the use of PSA testing and the aging population. The incidence is low in Eastern and South-Central Asia (age-standardised rates of 10.5 and 4.5, respectively), whilst rates in Eastern and Southern Europe, which were low, have showed a steady increase [55].

The Guideline for Prostate Cancer elaborated by the EAU [52] includes the three stages of the localized prostate cancer (low-risk, intermediate-risk, high-risk) that are defined as the probability of developing biochemical recurrence in localized prostate cancer (see Table 4-1).

Table 4-1: EAU risk groups for biochemical recurrence of localized and locally advanced prostate cancer

Localised			Locally advanced
Low-risk	Intermediate-risk	High-risk	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	any PSA any GS (any ISUP grade) cT3-4 or cN+

GS = Gleason Score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen

Gleason Score (GS) and International Society of Urological Pathology (ISUP) 2014 grade. The Gleason Score is the grading system used to determine the aggressiveness of prostate cancer. This grading system can be used to choose appropriate treatment options. The Gleason Score ranges from 1-5 and describes how much the cancer from a biopsy looks like healthy tissue (lower score) or abnormal tissue (higher score). (see Table 4-2),

The 2014, ISUP-endorsed grading system [56] limits the number of prostate cancer grades in order to: align the prostate cancer grading with the grading of other carcinomas; eliminate the anomaly that the most highly differentiated prostate cancer have a GS of 6; further define the clinically highly significant distinction between GS 7(3+4) and 7(4+3) prostate cancer [57].

Table 4-2: International Society of Urological Pathology 2014 grades

Gleason Score (GS)	ISUP grade
2-6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4 or 3+5 or 5+3)	4
9-10	5

Source: EAU. Guide for Prostate Cancer [52]

Most cancers score a grade of 3 or higher. The EAU guidelines development experts group [52] based their recommendations on evidence available in 2018 (see Table 4-3 and Table 4-4).

Table 4-3: EAU guidelines recommendations for the various disease stages [19, 52]

Prostate cancer stages. Recommendation.		**Strength rating**
Low-risk disease		
Radiotherapeutic treatment	Offer low-dose rate (LDR) brachytherapy to patients with low-risk prostate cancer, without a previous transurethral resection of the prostate (TURP) and with a good International Prostatic Symptom Score (IPSS) and a prostate volume < 50 mL.	Strong
	Use intensity-modulated radiation therapy (IMRT) with a total dose of 74-80 Gy or moderate hypofractionation (60 Gy/20 fx in four weeks, or 70 Gy/28 fx in six weeks), without androgen deprivation therapy (ADT).	Strong
Intermediate-risk disease		
Radiotherapeutic treatment	Offer LDR brachytherapy to selected patients; patients without a previous TURP and with a good IPSS and a prostate volume < 50 mL.	Strong
	For external-beam radiation therapy (EBRT), use a total dose of 76-78 Gy or moderate hypofractionation (60 Gy/20 fx in four weeks or 70 Gy/28 fx in six weeks), in combination with short-term neoadjuvant plus concomitant ADT (four to six months).	Strong
	In patients not willing to undergo ADT, use an escalated dose of EBRT (76-80 Gy) or a combination with brachytherapy.	Weak
High-risk localized disease		
Radiotherapeutic treatments	In patients with high-risk localized disease, use ERBT with 76-78 Gy in combination with long-term ADT (two to three years).	Strong
	In patients with high-risk localized disease, use EBRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT (two to three years).	Weak
Locally advanced disease		

Radiotherapeutic treatments	In patients with locally advanced cN0 disease, offer radiotherapy in combination with long-term ADT.	Strong
	Offer long-term ADT for two to three years.	Weak
Adjuvant treatment after radical prostatectomy		
	Discuss three management options with patients with pN+ disease after an ePLND, based on nodal involvement characteristics: 1. Offer adjuvant ADT for node-positive (pN+). 2. Offer adjuvant ADT with additional RT. 3. Offer observation (expectant management) to a patient after eLND and < 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension.	Weak
Non-curative or palliative treatments in a first-line setting		
Locally advanced disease		
PSA relapse after radical prostatectomy		
	Treat men with no evidence of metastatic disease with salvage radiotherapy (SRT) with additional hormonal therapy.	Weak

- intermediate-risk disease = When managed with non-curative intent, intermediate-risk prostate cancer is associated with ten-year and fifteen-year prostate cancer specific mortality rates of 13.0% and 19.6%, respectively.
- high-risk localised disease = Patients with high-risk prostate cancer are at an increased risk of PSA failure, need for secondary therapy, metastatic progression and death from prostate cancer. Nevertheless, not all high-risk prostate cancer patients have a uniformly poor prognosis after radical prostatectomy. When managed with non-curative intent, high-risk prostate cancer is associated with ten-year and fifteen-year prostate cancer specific mortality rates of 28.8% and 35.5%, respectively. There is no consensus regarding the optimal treatment of men with high-risk prostate cancer.
- locally advanced prostate cancer = No standard treatment can be defined in the absence of level 1 evidence. But a local treatment combined with a systemic one provides the best outcome, provided the patient is ready and fit enough to receive both. The optimal local treatment is still a matter of debate. Randomized controlled trials are only available for EBRT.

Table 4-4: Guidelines for metastatic disease, second-line and palliative treatments [52]

Recommendations		**Strength rating**
Metastatic disease in a first-line setting		
All M1 patients	Offer surgery and/or local radiotherapy to any patient with M1 disease and evidence of impending complications such as spinal cord compression or pathological fracture.	Strong
	Offer castration combined with prostate radiotherapy to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED (ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) criteria.	Weak
	Do not offer castration combined with any local treatment (radiotherapy/surgery) to patients with high volume M1 disease outside of clinical trials (except for symptom control).	Strong
	Offer castration alone, with or without an anti-androgen, to patients unfit for, or unwilling to consider, castration combined with docetaxel or abiraterone acetate plus prednisone or prostate radiotherapy.	Strong
Biochemical recurrence after treatment with curative intent		
Biochemical recurrence after radical prostatectomy	Offer AS and possibly delayed SRT to patients with biochemical recurrence and classified as EAU low-risk group at relapse who may not benefit from intervention.	Strong
	Treat patients with a PSA rise from the undetectable range with salvage radiotherapy. Once the decision for SRT has been made, SRT (at least 66 Gy) should be given as soon as possible.	Strong
	Offer no regional lymph node metastasis patients undergoing SRT hormonal therapy (with bicalutamide 150 mg for two years, or luteinising hormone-releasing hormone agonists for up to two years).	Weak

	Do not offer hormonal therapy to every no regional lymph node metastasis patient treated with SRT.	Strong
Biochemical recurrence after RT	Treat highly selected patients with localized prostate cancer and a histologically proven local recurrence with SRT.	Weak
	SRT should only be performed in experienced centres.	Strong
	Do not offer high-intensity focused ultrasound, cryosurgical ablation and salvage brachytherapy to patients with proven local recurrence since it is still experimental.	Strong
Life-prolonging treatments of castration-resistant disease		
Treat patients with metastatic castration-resistant prostate cancer with life-prolonging agents. Base the choice of first-line treatment on the performance status, symptoms, comorbidities, location and extent of disease, patient preference, and on the previous treatment for hormone-sensitive prostate cancer (alphabetical order: abiraterone, docetaxel, enzalutamide, radium-223, sipuleucel-T).		Strong
Cytotoxic treatments of castration-resistant disease		
Offer patients with metastatic castration-resistant prostate cancer and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide and radium-223.		Strong
Supportive care of castration-resistant disease		
In patients with spinal cord compression, start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.		Strong

ICD Classification:
Malignant neoplasm of prostate C61, C79.82, Z79.81, C79.49, Z85.46, R97.21, D07.5
Radiotherapy Z51.89, D01, D71. D81, D91, DB1, DD1, DF1, DG1, DM1, DT1, DU1, DV1, DW1
Mesh-terms (Medical Subject Headings): prostatic neoplasms

[A0003] – What are the known risk factors for prostate cancer?

Risk factors [19, 52]

A wide variety of exogenous or environmental factors have been discussed as being associated with the risk of developing prostate cancer or as being aetiologically important for the progression from latent to clinical prostate cancer [58]. Some of those are discussed below:

Metabolic syndrome (MetS)

The metabolic syndrome is a cluster of conditions that occur together, increasing the risk of heart disease, stroke and type 2 diabetes. These conditions include increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels. The single components of MetS, namely hypertension and waist circumference >102 cm, have been associated with a significantly greater risk of prostate cancer. In contrast, having >3 components of MetS is associated with a reduced risk (OR: 0.70, 95% CI: 0.60-0.82) [59].

- Diabetes/metformin. On a population level, metformin users (but not other oral hypoglycaemic agents) were found to be at a decreased risk of prostate cancer diagnosis compared with never-users [60]. In 540 diabetic participants of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study, metformin use was not significantly associated with prostate cancer and therefore not advised as a preventive measure.[61] The ongoing Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial assesses metformin use in advanced prostate cancer [62].

- Cholesterol/statins. A meta-analysis of fourteen large prospective studies did not show an association between blood total cholesterol, high-density lipoprotein cholesterol, low-density

lipoprotein cholesterol levels and the risk of either overall prostate cancer or high-grade prostate cancer [63]. Results of the REDUCE study also did not show a preventive effect of statins on prostate cancer risk [61].

- Obesity. Within the REDUCE study, obesity was associated with lower risk of low-grade prostate cancer, but increased risk of high-grade prostate cancer [64].

Dietary factors

The associations between a wide variety of dietary factors and prostate cancer have been studied (Table 4-5).

Table 4-5: Dietary factors that have been associated with prostate cancer [52]

Alcohol	High alcohol intake, but also total abstention from alcohol, have been associated with a higher risk of prostate cancer and prostate cancer-specific mortality. A meta-analysis shows a dose-response relationship with prostate cancer.
Dairy	A weak correlation between high intake of protein from dairy products and the risk of prostate cancer was found.
Fat	No association between intake of long-chain omega-3 poly-unsaturated fatty acids and prostate cancer was found. A relation between intake of fried foods and risk of prostate cancer may exist.
Tomatoes (lycopenes / carotenes)	Randomized controlled trials comparing lycopene with placebo did not identify a significant decrease in the incidence of prostate cancer.
Meat	A meta-analysis did not show an association between red meat or processed meat consumption and prostate cancer.
Phytoestrogens	Phytoestrogen intake was significantly associated with a reduced risk of prostate cancer in a meta-analysis.
Soy (phytoestrogens (isoflavones / coumestans))	Total soy food intake has been associated with reduced risk of prostate cancer, but also with increased risk of advanced disease.
Vitamin D	A U-shaped association has been observed, with both low and high vitamin-D concentrations being associated with an increased risk of prostate cancer, and more strongly for high-grade disease.
Vitamin E / Selenium	An inverse association of blood, but mainly nail selenium levels (reflecting long-term exposure), with aggressive prostate cancer has been found. Selenium and Vitamin E supplementation were, however, found not to affect prostate cancer incidence.

Source: European Association of Urology: EAU Guidelines

Hormonally active medication [52]

- 5-alpha-reductase inhibitors (5-ARIs). Although it seems that 5-ARIs have the potential of preventing or delaying the development of prostate cancer (~25%, for ISUP grade 1 cancer only), this must be weighed against treatment-related side effects as well as the potential small increased risk of high-grade prostate cancer. None of the available 5-ARIs have been approved by the European Medicines Agency for chemoprevention.

- Testosterone. Hypogonadal men receiving testosterone supplements do not have an increased risk of prostate cancer. A study showed that men with very low concentrations of free testosterone (lowest 10%) have a below average risk of prostate cancer [65].

Other potential risk factors were associated with high risk of prostate cancer: balding, gonorrhoea, occupational exposure (night-shift work, cadmium), current cigarette smoking, positive human papillomavirus [66].

A number of other factors previously linked to an increased risk of prostate cancer have been disproved, including vasectomy [67] and self-reported acne [68]. There are conflicting data about the use of aspirin or non-steroidal anti-inflammatory drugs and the risk of prostate cancer and mortality [69].

Genetic factors [52]**:** Family history and racial/ethnic background are associated with an increased prostate cancer incidence, suggesting a genetic predisposition. For men with relatives with prostate cancer, their age-specific increased risk of prostate cancer can be estimated. The probability of high-risk prostate cancer at age 65 was 11.4% (vs a population risk of 1.4%) in men whose father and two brothers had been diagnosed with prostate cancer in a Swedish population-based study. PSA testing mainly inflates detection of less relevant, any-risk prostate cancer.

Only a small subpopulation of men with prostate cancer (~9%) have true hereditary disease [70]. This is defined as three or more affected relatives or at least two relatives who have developed early-onset prostate cancer (< 55 years). Men with one first-degree relative diagnosed with prostate cancer have 1.8 times greater likelihood of having prostate cancer than the general population, whereas men with a father and brother or two brothers diagnosed with prostate cancer have a 5.51 times and 7.71 times greater likelihood respectively.

Hereditary prostate cancer is associated with a six to seven year earlier disease onset but the disease aggressiveness and clinical course does not seem to differ in other ways. Men of African descent show a higher incidence of prostate cancer and generally have a more aggressive course of disease [71].

Specific ancestry-specific risk loci have been identified. Of the underlying determinants of genomic diversity and mechanisms between genetic and environmental factors, much remains unknown. Genome-wide association studies have identified more than 100 common susceptibility loci contributing to the risk for prostate cancer [72].

Furthermore, among men with metastatic prostate cancer, an incidence of 11.8% was found for germline mutations in genes mediating DNA-repair processes. Germline mutations in genes such as BRCA1/2 and HOXB13 have been associated with an increased risk of prostate cancer and targeted genomic analysis of these genes could offer options to identify families at high risk. Prostate cancer screening trials targeting BRCA mutation carriers are ongoing. BRCA mutation carriers were reported to have worse outcomes when compared to non-carriers after local therapy. The association between genetic factors and the risk of (aggressive) prostate cancer is recognized but ongoing trials will need to define the clinical applicability of screening for genetic susceptibility to prostate cancer.

[A0004] – What is the natural course of prostate cancer?

Pattern of growth and spread. Prostate cancer is the development of cancer (abnormal cells) in the prostate gland of the male reproductive system that grow in an uncontrolled way. It can take many forms and is often benign, with most prostate cancer cells growing slowly and not likely to spread outside the prostate, while more aggressive forms spread quickly to other parts of the body which can be life threatening [73]. Prostate cancer usually does not have patient symptoms until the cancer has grown large enough to press against the urethra affecting urinary excretion from the bladder [73].

The most important predictors for the progression of prostate cancer include the clinical stage prognosis (TNM staging – see Table 4-6) combined with Gleason Score (cancer aggressiveness determined by specimen biopsy) and serum PSA (screening test).

Table 4-6: Clinical Tumour Node Metastasis (TNM) classification of prostate cancer [74]

T - Primary Tumour (stage based on digital rectal examination [DRE] only)		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Clinically inapparent tumour that is not palpable	
	T1a	Tumour incidental histological finding in 5% or less of tissue resected
	T1b	Tumour incidental histological finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA])
T2	Tumour that is palpable and confined within the prostate	
	T2a	Tumour involves one half of one lobe or less
	T2b	Tumour involves more than half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule	
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall	
N - Regional (pelvic) Lymph Nodes[1]		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
M - Distant Metastasis[2]		
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

[1]Metastasis no larger than 0.2 cm can be designated pNmi.
[2]When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category

Clinical T stage only refers to digital rectal examination findings; imaging findings are not considered in the TNM classification. Pathological staging (pTNM) is based on histopathological tissue assessment and largely parallels the clinical TNM, except for clinical stage T1c and the T2 substages. All histopathologically confirmed organ-confined prostate cancers after radical prostatectomy are pathological stage T2 and the current Union for International Cancer Control (UICC) no longer recognizes pT2 substages [74].

In accordance with the TNM staging system, localised prostate cancer includes low- and intermediate-risk cancer that has been staged as T1 or T2a or T2b (confined to the prostate gland) and locally advanced prostate cancer to include high-risk cancer as clinical stage T2c or more or with PSA over 20 ng/ml, or GS 8 to 10 [75].

In the TNM staging system, T3 means the cancer has broken through the capsule covering the prostate gland (number stage 3) and T4 means the cancer has spread to other organs of the body (number stage 4) [73]. The metastatic prostate cancer is the same type of cancer as the primary tumour; the tumoural cells spread to other organs of the body through tissue (by growing into nearby areas), the lymph system, and the blood.

Pattern of recurrence after local therapy. Available data suggests that within 10 years after surgery, one third of men will have evidence of recurrent disease [76]. Adjuvant radiation may be offered to these patients and has been shown to reduce the risk of local and PSA recurrence as well as clinical progression [77].

Biochemical recurrence after prostatectomy is defined as a PSA of ≥0.2 ng/mL on two separate tests. Data indicates that salvage radiotherapy is most effective when administered with a low PSA, i.e. 0.5 to 1.5 ng/mL [78].

Nomograms can provide patients and physicians with objective information to select treatment plans and estimate risk. Specifically, pre-prostatectomy nomograms predict the risk of adverse pathologic features, as well as of disease recurrence.

The risk of recurrence can be appreciated by using different tools or models: Kattan nomogram and University of California, San Francisco (UCSF) CAPRA score, D'Amico classification, UCSF-CAPRA score, PSA doubling time (PSADT).

Effects of the disease or health condition

[A0005] – What are the symptoms and the burden of prostate cancer for the patient?

a. Clinical presentation. Prostate cancer usually does not have patient symptoms until the cancer has grown large enough to press against the urethra, affecting urinary excretion from the bladder [73]. Unfortunately, there are usually no early warning signs for prostate cancer. The growing tumour does not push against anything to cause pain, so for many years the disease may be silent.

In rare cases, prostate cancer can cause symptoms, and these are overlaid with the symptoms in other benign disease (prostatitis or benign prostatic hypertrophy). A need to urinate frequently, especially at night, sometimes urgently; difficulty starting or holding back urination; weak, dribbling, or interrupted urination; painful or burning urination; difficulty in having an erection; a decrease in the amount of fluid ejaculated; painful ejaculation; blood in the urine or semen; pressure or pain in the rectum; pain or stiffness in the lower back, hips, pelvis, or thighs.

b. Clinical diagnosis. Prostate cancer is usually suspected on the basis of digital rectal examination and/or PSA levels. Definitive diagnosis depends on histopathological verification of adenocarcinoma in prostate biopsy cores or specimens from TURP or prostatectomy for benign prostatic enlargement.

c. Quality of life [52]
Overall quality of life (QoL) in men with prostate cancer. Living longer with prostate cancer does not necessarily equate to living well. There is clear evidence of unmet needs and ongoing support requirements of some men after diagnosis and treatment for prostate cancer. Cancer impacts on the wider family and cognitive behavioural therapy can be a strategy to help reduce depression, anxiety and stress in caregivers. Radical treatment for prostate cancer can negatively impact long-term quality of life (e.g. sexual, urinary and bowel dysfunction), as can ADT used in short- or long-term treatment, e.g. sexual problems, fatigue psychological morbidity, adverse metabolic sequelae, increased cardiovascular and bone fracture risk. Direct symptoms from advanced or metastatic cancer, e.g. pain, hypercalcaemia, spinal cord compression, pathological fractures, also adversely affect health. Men's QoL including domains such as sexual function, urinary function and bowel function, is worse after treatment for prostate cancer compared to non-cancer controls. In this regard, specific tools or patient-reported outcome measures have been developed and validated for men with prostate cancer [19].

Long term (>12 months) quality of life outcomes in men with localized disease. The findings regarding radical prostatectomy and radiotherapy are supported by observational studies (the Prostate Testing for Cancer and Treatment – ProtecT- trial), the Prostate Cancer Outcomes Study where results after five years of follow-up show that men who underwent radical prostatectomy had a higher prevalence of urinary incontinence and erectile dysfunction (ED), while men treated with radiotherapy had a higher prevalence of bowel dysfunction. However, there were no significant differences in the adjusted odds of urinary incontinence, bowel dysfunction or ED between radical prostatectomy and radiotherapy at fifteen years [79].

Therapeutic alternatives and QoL
An effective therapeutic plan aiming the improving of QoL should be focused on the patient's needs (physical and mental, work or vocation, psychosocial) and personalised care could

represent an appropriate solution. Prostate cancer care should not be reduced to focusing on the organ in isolation: side effects or late adverse effects of treatment can manifest systemically and have a major influence on the patient's QoL.

- Surgery. Wide variation in the types of complications is reported: ED and other (dry ejaculation, change in the quality of orgasm and occasional pain on orgasm, penile length); long-term incontinence but voiding difficulties may also occur associated with bladder neck contracture. For those men undergoing minimally invasive procedures port site hernia has been reported in 0.66% after inserting 12 mm bladeless trocar and can occur more rarely with 8 mm and 5 mm trocars [80].

- Radiotherapy. A systematic review and meta-analysis of case control studies comparing patients exposed or unexposed to radiotherapy in the course of treatment for prostate cancer demonstrate an increased risk of developing second cancers for bladder, colorectal and rectum with similar risks over lag times of five and ten years.

> **EBRT:** EBRT + ADT 6 months (bowel toxicity including persistent diarrhoea, bowel urgency and/or incontinence and rectal bleeding; 3D CRT and IMRT demonstrate less bowel toxicity than noted previously with 3D CRT (ProtecT study) [81].
>
> **Brachytherapy -** urinary complications following implantation, such as urinary retention (1.5-22%), with post-implantation TURP reported as being required in up to 8.7% of cases, and incontinence (0-19%) [82]; chronic urinary morbidity (<20% of patients), depending on the severity of the symptoms before brachytherapy.

Other adverse effects of prostate cancer therapies [20]

- *Sexual function***.** Cessation of sexual activity is very common in men undergoing ADT, affecting up to 93% of men as ADT reduces both libido and the ability to gain and maintain erections.

- *Hot flushes.* Hot flushes are a common side- effect of ADT (prevalence estimated between 44-80% of men on ADT). They appear three months after starting ADT, usually persist long-term and have a significant impact on QoL. Oestrogen-receptor modulators or low-dose oestrogen therapies, e.g. diethylstilbestrol, 0.5-1 mg/day, reduce the frequency and severity of hot flushes. Both treatments carry a risk of cardiovascular complications.

- *Non-metastatic bone fractures.* Due to increased bone turnover and decreased bone mineral density in a time-dependent manner, ADT use is linked to an increased risk of fracture; hip fractures in men are associated with a significant risk of death; obesity (increase in body fat mass by up to 10%) and sarcopenia (decrease in lean tissue mass by up to 3%) as well as weight loss are common and occur during the first year of ADT, and these changes increase the fracture.

- *Metabolic effects.* Lipid alterations are common and may occur as early as the first three months of treatment. ADT also decreases insulin sensitivity and increases fasting plasma insulin levels, which is a marker of insulin resistance. In patients with diabetes, metformin appears to be an attractive option for protection against metabolic effects based on retrospective analysis, but there is insufficient data to recommend its use in patients without diabetes.

Metabolic syndrome is an association of independent cardiovascular disease risk factors, often associated with insulin resistance. The prevalence of a metabolic-like syndrome is higher during ADT compared with men not receiving ADT.

- *Cardiovascular morbidity*. After only six months of treatment, ADT was associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction. An increase in cardiovascular mortality has been reported in patients suffering from previous congestive heart failure or myocardial infarction in a retrospective database analysis [83] or presenting with a metabolic syndrome [84].

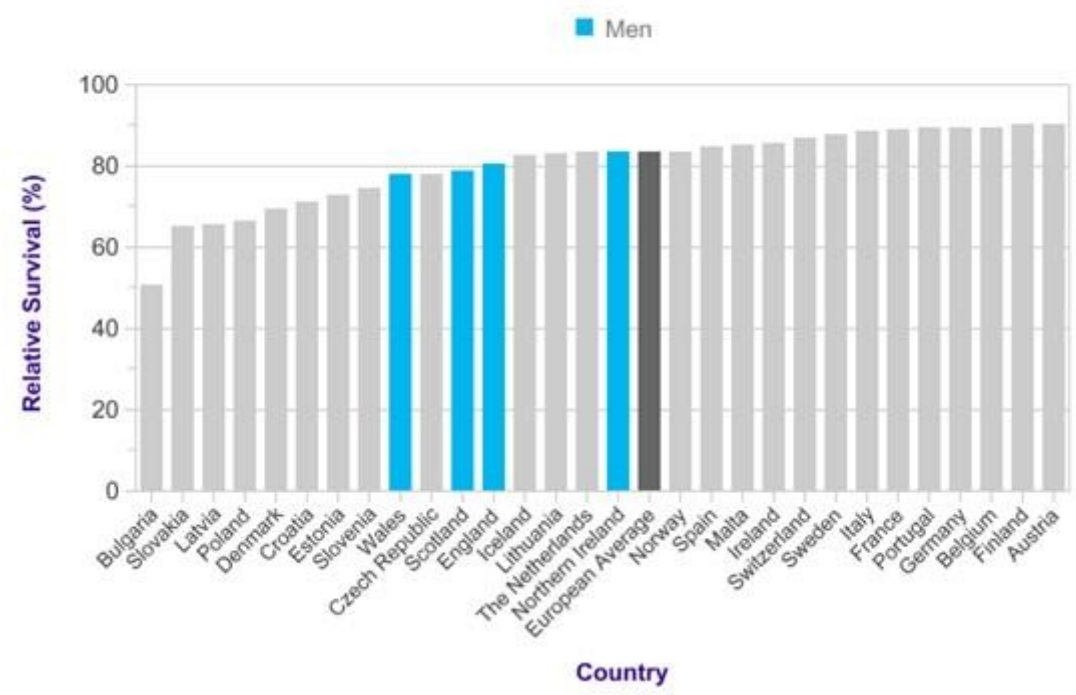
- *Fatigue.* Fatigue often develops as a side effect of ADT and anaemia may be a cause of fatigue requiring etiological diagnosis and individualised treatment.

Neurological side effects - Castration also seems to be associated with an increased risk of stroke and is suspected of being associated with an increased risk for depression and cognitive decline such as Alzheimer's disease [85].

[A0006] – What are the consequences of prostate cancer for society?

In Europe, as Figure 4-1 below shows, the prostate cancer 5-year relative survival rate is 83% [86], ranging from 51% (Bulgaria) to 90% (Austria).

Figure 4-1: Age standardized 5-year relative survival, Men (aged 15+). European countries prostate cancer 2000-2007



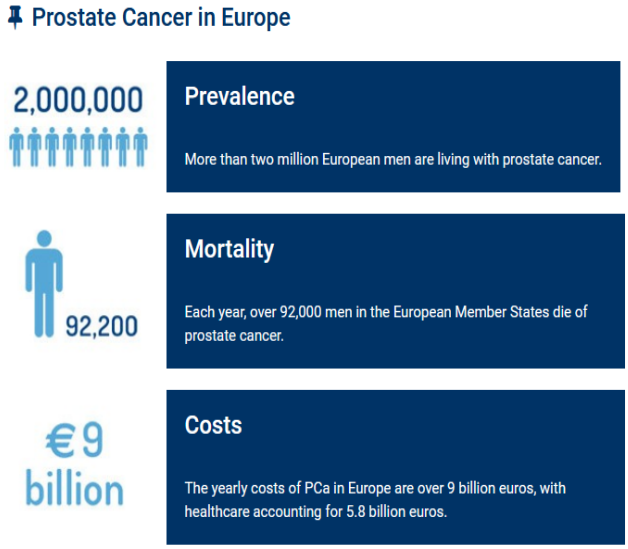
Source: Cancer Research UK, image available at link: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/survival#heading-Four

"Saving lives and ensuring a high quality of life requires immediate European actions" [87] could reflect the current concern and European efforts in the field of reducing the impact of prostate cancer at individual and societal level. Radiotoxicity and the persistence of symptoms can significantly reduce patients' QoL, and with patients generally living for many years after prostate cancer treatment, protection of their QoL is of utmost importance.

More than two million Europeans are living with prostate cancer; each year, over 92,000 men in Europe die of prostate cancer; and each year, cases of prostate cancer in Europe cost over 9 billion euros, of which 5.8 billion euros represents the cost for health care services (see Figure 4-2).

The trend and the level of impact on society led to dedicating a special day (22 January 2019) when policy makers, scientific experts, European associations working in the urological field and representatives of European patient groups with an interest in prostate disease rediscussed how early diagnosis will improve outcomes in European prostate cancer patients and covered key topics such as the latest evidence, consequences of not performing PSA screening, overdiagnosis and overtreatment [87].

Figure 4-2: Impact of prostate cancer, Europe, 2018 [87]



Source: Image retrieved from public domain, namely European Prostate Cancer Awareness Day [87]

Current clinical management of the disease or health condition

[A0024] – How is prostate cancer currently diagnosed according to published guidelines and in practice?

Definitive clinical diagnosis depends on histopathological verification of adenocarcinoma in prostate biopsy cores or specimens from TURP or prostatectomy for benign prostatic enlargement. The most common way that clinicians diagnose prostate cancer is through the TNM staging system which include four stages of tumour development (T1 to T4) that describe the size of the tumour (T), whether there are any cancer cells in the lymph nodes (N) and whether the cancer has spread to other parts of the body (M) [73]. Clinicians may also use a number staging system to define prostate cancer into four stages (Stage 1 to Stage 4).

Ultrasound (US)-guided biopsy [52] is now the standard of care for diagnosing prostate cancer. Prostate biopsy is performed by either the transrectal or transperineal approach. Cancer detection rates, when performed without prior imaging with MRI, are comparable between the two approaches [88], although some evidence suggests reduced infection risk with the transperineal route. Rectal disinfection with povidone-iodine may be considered [89]. TURP should not be used as a tool for cancer detection [53].

Prior to performing a prostate biopsy, the EAU recommends the use of other tools such as a risk-calculator, imaging or an additional serum or urine-based test in men with a normal digital rectal examination and a PSA, in order to avoid unnecessary consumption of resources.

Other imaging procedures (transrectal ultrasound (TRUS), sonoelastography and contrast-enhanced ultrasound) are still limited by lack of standardisation, lack of large evaluation and unclear results in transition zones. Multiparametric magnetic resonance imaging (mpMRI) is increasingly used to localize suspicious areas that could be targeted by so-called magnetic resonance imaging-targeted biopsies (MRI-TBx).

MRI-TBx can be used in two different diagnostic pathways: 1) the ‘combined pathway’, in which patients with a positive mpMRI undergo combined systematic and targeted biopsy, and patients with negative mpMRI undergo systematic biopsy; 2) the ‘MR pathway’, in which patients with a positive mpMRI undergo only MRI-TBx, and patients with negative mpMRI are not biopsied at all.

MRI-TBx substantially improve the detection of ISUP grade > 2 prostate cancer. This improvement iqs most notable in the repeat-biopsy setting, with marginal added value for

systematic biopsies. It is less marked in biopsy-naïve patients in whom systematic biopsy retains a higher added value, at least for the detection of ISUP grade 2 cancers. MRI-TBx also detect significantly less ISUP grade 1 cancers than systematic biopsies.

The 'MR pathway' is appealing since it could decrease the number of biopsy procedures, reduce the detection of low-grade prostate cancer while maintaining (or even improving) the detection of CS prostate cancer, as compared to systematic biopsy [19, 52].

[A0025] – How is prostate cancer currently managed according to published guidelines and in practice?

The current concerns in the field of efficient management of prostate cancer are based on essential elements aiming to: provide the population with screening and early detection programmes and tools, stratify the population in risk groups, provide treatment options and patient-specific treatment plans, provide specific management alternatives for different stages (localized and locally advanced prostate cancer, recurrence after local therapy), reduce the adverse effects of the medication. It is also a concern to find ways of including patient-reported outcome measures and patient information about treatments.

Screening and early detection of prostate cancer
Currently, *screening* for prostate cancer is one of the most controversial topics in the urological literature [90]. There is no standard test to screen for prostate cancer, but two tests are commonly used [91]: PSA test and digital rectal examination. A comparison of systematic and opportunistic screening suggested over-diagnosis and mortality reduction in the systematic screening group compared to a higher over-diagnosis with a marginal survival benefit, at best, in the opportunistic screening regimen [92].

Early detection of prostate cancer has the aim of detecting the disease in the earliest stages and to allow for effective interventions for men at risk of developing prostate cancer. An individualised risk-adapted strategy for early detection might be offered to a well-informed man with at least ten to fifteen years of life expectancy. It is important to carefully identify the patient, taking into account the potential balances and harms involved. However, this approach may still be associated with a substantial risk of over-diagnosis [19, 52].

Risk calculators may be useful in helping to determine (on an individual basis) what the potential risk of cancer may be, thereby reducing the number of unnecessary biopsies. Several tools developed from cohort studies are available including:

- the Prostate Cancer Prevention Trial cohort: PCPTRC 2.0
- the European Randomized Study of Screening for Prostate Cancer cohort:
- a Canadian cohort

None of these risk calculators has clearly shown superiority, and in this regard it remains a personal decision as to which one to use [93].

Risk stratification of clinically localized prostate cancer (Table 4-7) has served as a guide to counsel patients on treatment options. Integration of tumour biology with clinical practice may lead to a more individualized, patient-specific treatment plan.

Table 4-7: Adapted risk stratification for people with localized & locally advanced prostate cancer [20, 73]

	Level of risk	PSA		Gleason Score		TNM staging system	Number staging system
Localized prostate cancer	Low risk	<10 ng/ml	and	≤6	and	T1 to T2a	Stage 1 (N=0, M=0)
	Intermediate risk	10-20 ng/ml	or	7	or	T2b	Stage 2

Locally advanced prostate cancer	High risk	>20 ng/ml	or	8-10	or	≥T2c	(N=0, M=0)

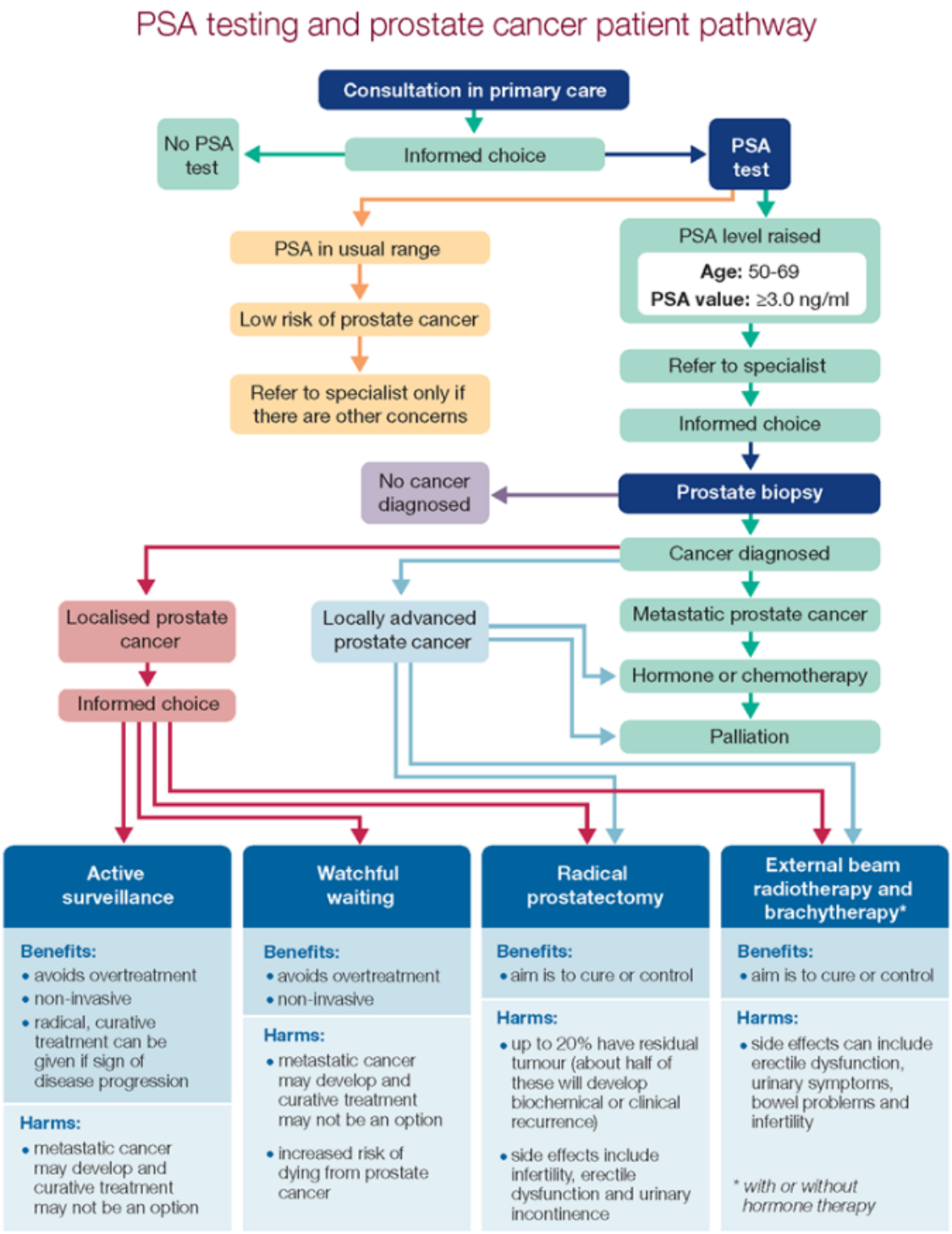
PSA; prostate-specific antigen; N: cancer cells to lymph nodes; M: cancer cells to other parts of the body

Treatment. After biopsy-diagnosed prostate cancer, as illustrated in Figure 4-3 below, NICE recommends multiple treatment options, with their respective benefits and harms to include: active surveillance (AS)*, watchful waiting**, radical prostatectomy, EBRT and brachytherapy [94]. *AS aims to avoid unnecessary treatment in men with clinically localized prostate cancer who do not require immediate treatment, but at the same time achieve the correct timing for curative treatment in those who eventually do [95].

** Watchful waiting refers to conservative management for patients deemed unsuitable for curative treatment right from the outset, and patients are 'watched' for the development of local or systemic progression with (imminent) disease-related complaints, at which stage they are then treated palliatively according to their symptoms, in order to maintain QoL.

In the current context, the clinical management of the prostate cancer is complex and the curative approach includes radiotherapy as one key therapy (surgery being the second one) that could be applied as active treatment [20]. It is recommended that patients with localized and locally advanced prostate cancer receiving radical curative EBRT are offered planned treatment techniques that optimize the dose to the tumour while minimizing the risks of normal tissue damage [20]. Patients undergoing EBRT may receive fiducial markers (small metal seeds implanted into the prostate to assist effective targeting of radiotherapy), depending on local practice. Based on CT planning scan and MRI, dosimetry plans for radiotherapy delivery are created by the dosimetrist and signed off by the radiation oncologist, and radiotherapy is then delivered according to the treatment plan.

Figure 4-3: PSA testing and prostate cancer patient pathway



Source: image retrieved from public domain:PSA testing and prostate cancer patient pathway www.gov.uk/guidance/prostate-cancer-risk-management-programme-overview

Target population

[A0007] – What is the target population of this assessment?

The main target population of this assessment is represented by patients who have a prostate cancer diagnosis and receive radiotherapy with curative intent, meaning radical doses of radiotherapy, either for first-time and recurrent cancer.

In this regard, the 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 radiotherapy; and those at higher baseline risk of rectal toxicity [19].

The target population for Barrigel™ and for the SpaceOAR™ Hydrogel System, is patients receving radical radiotherapy for prostate cancer. The target population may be the population identified in the authorisation or a target group of patients using the technology for which the company wants reimbursement. The primary target group population to obtain reimbursement could include patients with localized prostate cancer clinical stages T1 – T2.

Although not the target population described above, it is important to note that several observational studies have demonstrated patient benefits in patient groups extending to T3a patients (high-risk localized and/or locally advanced prostate cancer) [45, 96, 97].

[A0023] – How many people belong to the target population?

Expert opinion suggests the majority of patients diagnosed with prostate cancer (approximately 90%) are those who have cancer confined to the prostate gland (clinically localized disease, clinical stages T1-T3a). Furthermore, European cancer registries/studies suggest that around half of radiotherapy patients have low/intermediate risk localized prostate cancer.

Based on the above description, Boston Scientific has estimated the target population numbers for Europe, in 2018, as follows (see Table 4-8). These numbers, however, are a reasonable estimate of size of the potential benefiting population for any biodegradable rectal spacer.

Table 4-8: Estimated target population for SpaceOAR™ in Europe in 2018

Item		ESTIMATES*	
	Potential Patients in Europe	No. of patients	% proportion
1	Number of localized prostate cancer patients undergoing radiotherapy	405,000	N/A
2	Number of localized prostate cancer patients undergoing radiotherapy, all risk stratifications	121,500-182,250	30%-45%**
3	Number of low/intermediate risk prostate cancer patients undergoing radiotherapy, T1 – T2	60,750-91,125	50%***

**Boston Scientific internal estimates from clinical expert opinion in the therapeutic area; N/A: not applicable; **30-45% is a proportion of item 1; ***50% is a proportion of item 2*

There is an increase in the target population expected over time with the increase in radiotherapy procedure for prostate cancer patients. This may be due in part to an aging population and an increase in diagnosis with the use of PSA testing allowing for younger and older men to be tested. According to the EAU, diagnosis is common in older men (median 68 years) and diagnosis in men > 65 will result in a 70% increase in annual diagnosis by 2030 in Europe and the United States.

[A0011] – How much are the technologies utilized?

Recently, research concerning spacer utilization has been focused on prostate cancer radiotherapy. After the first study involving hyaluronic acid (HA) as a spacer in prostate radiotherapy by Prada et al. in 2007 [98], there has been a rapidly increasing number of spacer studies including different spacer materials on this single disease entity [99].

In England, SpaceOAR™ was selected as a device under the Innovation and Technology Payment (ITP) scheme which allowed selected centres to order the technology free of charge from the company. The ITP programme launched by NHS runs a competitive process to find the most promising new tests and treatments, and makes them available to hospitals for free, removing cost as a barrier to adoption. The aim of this scheme was to accelerate access to innovative technologies. The 2019/20 ITP programme builds on the Innovation and Technology Tariff (ITT) and ITP 2018/19 and is supporting, among others, rectum spacers to reduce rectum radiation exposure during prostate radiation therapy [100].

The study by Müller et al (2016) based on multicentre experience acquired by radiation oncologists and urologists, each with experience of 23-138 SpaceOAR™ injections in prostate cancer patients before trying dose-escalated radiotherapy, aimed to reach a consensus on indication and application of a hydrogel spacer [101]. The user experience questions were formulated so to comprise practical information relevant for successful hydrogel injection and treatment. The main indication for hydrogel application was dose-escalated radiotherapy for histologically confirmed low- or intermediate-risk prostate cancer; it was not recommended in locally advanced prostate cancer. The injection or implantation was performed under transrectal ultrasound guidance via the transperineal approach after prior hydrodissection. The rate of injection-related G2-toxicity was 2% (n = 5) in a total of 258 hydrogel applications. The most frequent complication (n = 4) was rectal wall penetration, diagnosed at different intervals after hydrogel injection and treated conservatively. The reached consensus agreed on two points: current experience showed the feasibility of the application of a hydrogel spacer; the implementation of this method could be promoted in more centres in order to reduce radiation-related gastrointestinal toxicity of dose-escalated image-guided radiotherapy. As potential serious adverse events could not be excluded (even if their rate is very low), the application should be carefully discussed with the patient and the risk balanced against potential benefits.

5 CLINICAL EFFECTIVENESS (EFF)

5.1 Research questions

Element ID	Research question
[D0001]	What is the expected beneficial effect of biodegradable rectum spacers on toxicity during curative radiotherapy on mortality?
[D0005]	How do biodegradable rectum spacers affect symptoms and findings (severity, frequency) for prostate cancer?
[D0006]	How do rectum spacers affect progression (or recurrence) of prostate cancer?
[D0011]	What is the effect of biodegradable rectum spacers on patients' body functions?
[D0012]	What is the effect of biodegradable rectum spacers on generic health-related quality of life?
[D0013]	What is the effect of biodegradable rectum spacers on disease-specific quality of life?
[D0017]	Were patients satisfied with biodegradable rectum spacers?

5.2 Results

Included studies

For this domain we have used evidence from one RCT [4] and one nRCT [9]. Several companion publications and a trial registry record are associated to the RCT as table 2-1 has previously shown (i.e. NCT01538628 trial registry record, Pieczonka 2015 and Hamstra 2017 abstracts Pieczonka 2015, Fischer-Valuck 2017, Hamstra 2017, Hamstra 2018, and Karsh 2017 full text). From these, we used the trial registry record (NCT01538628) and the five full-text publications (Pieczonka 2015, Fischer-Valuck 2017, Hamstra 2017- 2018 and Karsh 2017). Follow-up times for the outcomes reported in Mariados 2015 and Pieczonka were 3 to 15 months, median of 3 years in Hamstra 2017-18, while Karsh and Fischer-Valuck 2017 was unclear.

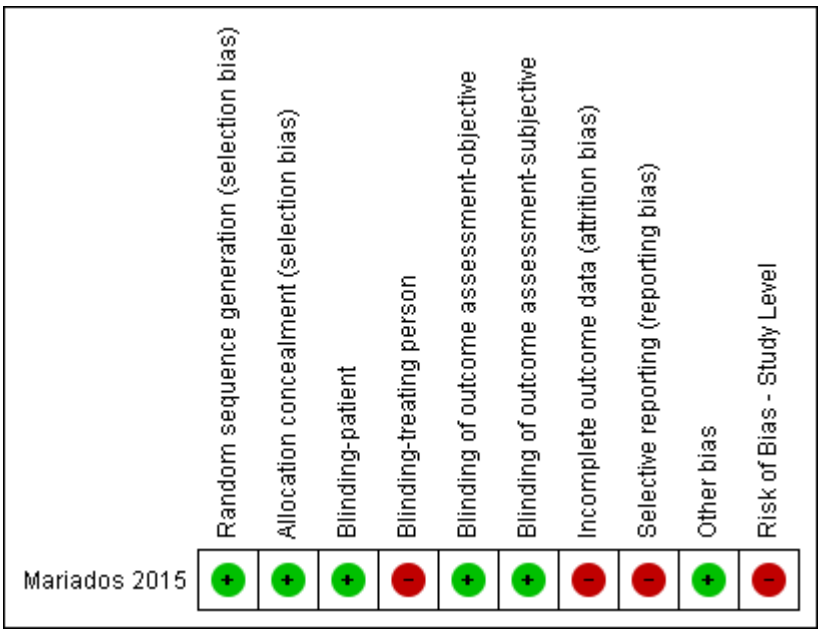
Mariados' RCT enrolled 222 patients from 20 centres in the United States. Patients with stage T1 or T2 prostate cancer were randomized to receive a SpaceOAR™ Hydrogel spacer+RT (n=149) or radiotherapy alone (control group) (n=73) (analysis per protocol). Baseline characteristics show similar mean age in the SpaceOAR™ group: 66.4 years; control group: 67.7 years (p=.2), and race (white: spacer 85%, control 84%, p=.8). Men were included if they had had a Gleason Score of <7, PSA concentration of 20 ng/ml, and a Zubrod performance status of 0–1, and were planning to have IG-IMRT. Baseline sexual QoL was poor (mean 53 ±24 standard deviation) defined as an EPIC score of ≤60) with 38% (80/123) having adequate sexual QoL and "erections firm enough for intercourse" – androgen deprivation was not allowed and no patients experienced biochemical failure or salvage therapy. The trial excluded men with a prostate volume of >80 cm3, extracapsular extension of disease or >50% positivity biopsy scores, metastatic disease, indicated for or had recent androgen deprivation therapy and prior prostate surgery or radiotherapy.

Wolf's [9] nRCT study was conducted in Austria. It included patients with prostate cancer (n=78, 30 SpaceOAR™ (or gel)+RT versus 29 ProSpace balloon+RT group versus 19 radiotherapy alone (control group) and followed them up for a total of 6 months. Participants' age and disease stage were not specified. For assessment of balloon spacer volume dynamics, a separate group of 18 patients who had the spacer were analysed. Men not eligible for spacer application because of intrinsic contraindications, such as compulsory anticoagulation therapy or severe co-morbidities preventing them from having anaesthesia, served as control group. Men with hip transplants were excluded from the study.

The overall judgement of the risk of bias for the RCT and nRCT was high risk. Figure 5-1 provides a summary of the risk of bias assessment for the Mariados et al. trial. Further details are available

in the risk of bias table included in Appendix 1 – Tables A6 and A7. The certainty of the evidence ranged from “low” to “very low” across study designs. The most common limitations of the evidence were: 1) serious risk of bias that reduced the level of confidence in the observed effects, and 2) imprecision (e.g., one or two small studies, uncertainty about the true magnitude of the effect). Common sources of bias included: 1) bias due to confounding 2) bias in selection of participants into the studies 2) bias in measurments of outcomes, 3) bias on blinding of treating personal 4) reporting bias, and 5) attrition bias. There was insufficient evidence for safety of rectum spacers. Reported (device) adverse events come from the RCT only and the rational behind their classificationa and the method of measuring them is unclear; we are unsure whether information was captured systematically across patients.

Figure 5-1: Risk of Bias for the RCT



Mortality

[D0001] – What is the expected beneficial effect on mortality of the biodegradable rectum spacers in addition to radiotherapy?

The expected beneficial effect of this technology on mortality was not measured and we were unable to answer this research question.

Morbidity

[D0005] – How does the technology affect symptoms and findings (severity, frequency) of prostate cancer?

The studies did not measure this outcome and we were unable to answer this research question. However, although in this assessment we considered rectal and urinary toxicity as effectiveness outcomes, it can be argued that clinicians are most concern with the morbidity caused by toxicity due to radiation therapy while treating prostate cancer.

[D0006] – How do biodegradable rectum spacers affect progression (or recurrence) of prostate cancer?

The studies did not measure this outcome and we were unable to answer this research question. But PSA relapse, if considered as a surrogate outcome, could signal prostate cancer recurrence. The insertion of rectum spacers could allow the delivering of higher radiation doses to the prostate affecting the disease progression.

[D0011] – What is the effect of biodegradable rectum spacers on patients' body functions?

In this section we describe rectal and urinary toxicity, rectal dose and increased distance between rectum and prostate as proxies for outcomes relating to body functions.

Toxicity
Acute and late rectal and urinary toxicity results are presented in Tables 5-1 to 5-6, with a high-level summary of findings in Table 5-7 below.

In the prospective multicentre RCT of 222 patients [4], the radiotherapy technique employed was IG-IMRT (79.2 Gy in 1.8 Gy fractions) with a follow-up of up to 15 months. The Hamstra 2017 companion study [6] involved 63% of the original sample at a median of approximately three years post-enrolment. In the nRCT [9], 78 patients were involved: SpaceOAR™ +RT (n=30) with biodegradable balloon spacer+RT (n=29) and radiotherapy alone/no spacer (n=19). The radiotherapy technique employed was IMRT (total dose of 75.85 Gy in daily 1.85 Gy fractional doses).

Acute rectal toxicity (3 months following radiotherapy):
Low certainty evidence shows the risk of developing grade 1 rectal toxicity was 23% lower (RR 0.77, 95% CI 0.50 to 1.19; p=.42; participants = 220) and the risk of developing grade 2 or greater was 9% lower (RR 0.91, 95% CI 0.24 to 3.5; p=.89; participants = 220) in individuals in the SpaceOAR™ +RT group than in the RT group. The differences between the SpaceOAR™ +RT and the RT groups for grade 1 and ≥2 acute rectal toxicity were not statistically significant (null value of 1 lies in the 95% CI). No grade 3 or 4 rectal toxicity was reported in the intervention+RT group. A single grade 3 case was reported among the RT group; no grade 4 reported. Fewer patients in the SpaceOAR™ +RT group had rectal pain (3% compared with 11% in the RT group, p=.02).

Table 5-1: Acute rectal toxicity – 3 months (Mariados 2015)

	Grade 0	Grade 1	Grade ≥2
SpaceOAR™ +RT	108	34	6
RT alone	49	20	3
RR [95% CI]		0.77 [0.50 to 1.19]	0.91 [0.24 to 3.48]
p value		p=.42	p=.89

CI: confidence interval; RT: radiotherapy; RR: risk ratio

Very low certainty evidence shows the risk of developing acute rectal toxicity of grade 1 was 58% lower in the RT group (RR 1.58, 95% CI 0.34 to 7.60; p=.55; participants = 49) when compared to SpaceOAR™ and 64% lower in the RT than in the balloon group (RR1.64, 95% CI 0.35 to 7.60; p=.52; participants = 48). The differences between the spacers+RT and the RT groups were not statistically significant (null value of 1 lies in the 95% CI). No other rectal toxicities were reported, but authors stated "overall acute toxicity was low with no grade 3 toxicity".

Table 5-2: Acute rectal toxicity – 3 months (Wolf 2015)

	Grade 0	Grade 1	Total	Effect size [95% CI]
SpaceOAR™ +RT	25	5	30	1.58 [0.34 to 7.60] p=.55
Balloon+RT	24	5	29	1.64 [0.35 to 7.60] p=.52
RT alone	17	2	19	

CI: confidence interval; RT: radiotherapy; RR: risk ratio

Late rectal toxicity
15 months – low certainty of the evidence suggests that the risk of developing rectal toxicity grade 1 was 66% lower in the SpaceOAR™ +RT group (RR 0.34, 95% CI 0.08 to 1.48; p=.16; participants = 220) and the risk of grade ≥2 was 85% lower in the SpaceOAR™ +RT group (RR 0.15, 95% CI 0.01 to 3.71; p=.25; participants = 220). The differences between the SpaceOAR™

+RT and the RT groups were not statistically significant (null value of 1 lies in the 95% CI). A single grade 3 case was reported at 15 months among the RT group, presumably the same case recorded at 3 months follow-up; no grade was 4 reported.

Table 5-3: Late rectal toxicity – 15 months (Mariados 2015)

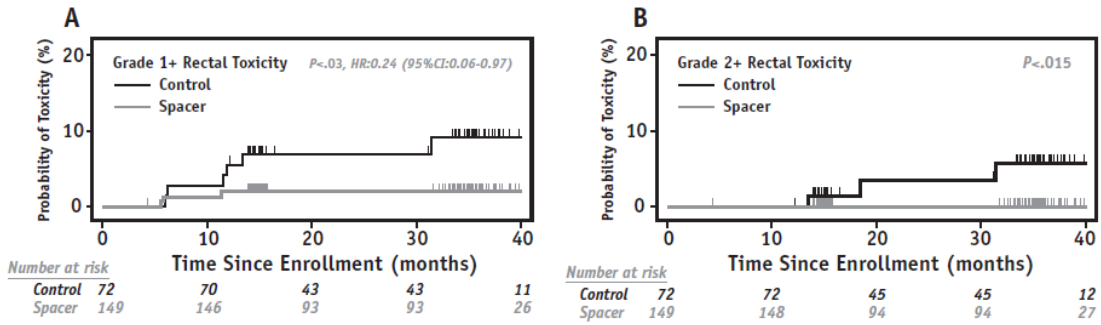
	Grade 0	Grade 1	Grade ≥2
SpaceOAR™ +RT	145	3	0
RT alone	66	4	2
RR [95% CI]		0.34 [0.08 to 1.48]	0.15 [0.01 to 3.71]
p value		p=.1669	p=.2521

CI: confidence interval; RT: radiotherapy; RR: risk ratio

Cumulative Incidence

Median of three years – very low certainty evidence from the RCT suggests that patients in the SpaceOAR™+RT group at any time point during the study period were 76% less likely to present grade 1 rectal toxicity than the RT group (HR 0.24, 95% CI 0.06 to 0.97; p<.03, participants = 140; see Figure 5-2). The HR was not presented for grade ≥2 toxicity as it was not possible to calculate. There was 1 case of grade 3 toxicity in the RT group, and no cases of grade 4 reported. The differences between SpaceOAR™ +RT and the control group for grade 1 acute and late rectal toxicity were statistically significant (null value of 1 does not lie in the 95% CI).

Figure 5-2: Cumulative incidence of grade 1 and ≥2 rectal toxicity



Source: Hamstra [6] (licensed under CC BY-NC-ND 4.0)

Acute urinary toxicity – up to 3 months

When comparing SpaceOAR™ +RT vs RT alone, low certainty evidence suggests that the risk of developing grade 1 urinary toxicity at 3 months was 2% lower in the RT group (RR 1.02, 95% CI 0.86 to 1.21; p=.74; participants = 220) and of developing grade ≥2 toxicity was 3% lower in the SpaceOAR™ +RT group (RR 0.97, 95% CI 0.80 to 1.17; p=.79; participants = 220).The differences between the SpaceOAR™ +RT and RT groups for all grades of urinary toxicity were not statistically significant (null value of 1 lies in the 95% CI). No grades 3 or 4 were reported.

Table 5-4: Acute urinary toxicity – 3 months (Mariados 2015)

	Grade 0	Grade 1	Grade ≥2
SpaceOAR™ +RT	14	78	56
RT alone	7	33	32
RR [95% CI]		1.02, [0.86 to 1.21]	0.97, [0.80 to 1.17]
p value		p=.74	p=.79

CI: confidence interval; RT: radiotherapy; RR: risk ratio

Very low certainty of evidence from the nRCT [9] suggests the risk of developing genitourinary grade 2 toxicities was 39% lower in the RT group when compared to gel (RR 1.39, 95% CI 0.57 to 3.38; p=.46; participants=49) but 21% lower in the balloon+RT group when compared to RT (RR

0.79, 95% CI 0.28 to 2.22; p=.64; participants = 48). The differences between either spacer and the RT group for genitourinary toxicity were not statistically significant (null value of 1 lies in the 95% CI). No grades 3 or 4 were reported.

Table 5-5: Acute urinaryToxicity – 3 months (Wolf 2015)

	Grade 0	Grade 2	Total	Effect size [95% CI]
SpaceOAR™ +RT	19	11	30	RR 1.39, [0.57 to 3.38] p=.4637
Balloon+RT	23	6	29	RR 0.78, [0.27 to 2.12] p=.64
RT alone	14	5	19	

CI: confidence interval; RT: radiotherapy; RR: risk ratio

Late urinary toxicity

15 months – low certainty of the evidence suggests the risk for grade 1 was 35% lower in the SpaceOAR™ +RT group (RR 0.65, 95% CI 0.15 to 2.85; p=.57; participants = 220). However, the risk for grade ≥2 toxicities was 57% lower in the RT group (RR 1.57, 95% CI 0.44 to 5.53; p=.47; participants = 220). The differences between the SpaceOAR™ +RT and the RT groups for grades 1 and ≥2 late urinary toxicity were not statistically significant (null value of 1 lies in the 95% CI). No grade 3 or 4 urinary toxicities were reported.

Table 5-6: Late urinary toxicity – 15 months (Mariados 2015)

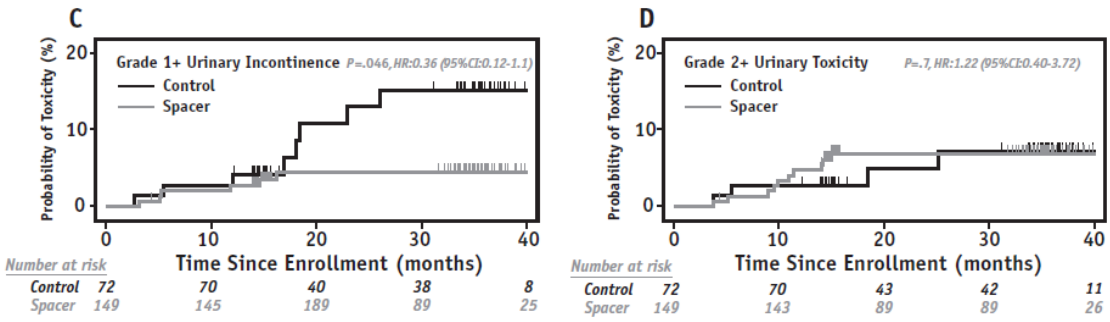
	Grade 0	Grade 1	Grade ≥2
SpaceOAR™ +RT	134	4	10
RT alone	65	3	3
RR		RR 0.65 [0.15 to 2.85]	RR 1.57 [0.44 to 5.53]
p value		p=.57	p=.47

CI: confidence interval; RT: radiotherapy; RR: risk ratio

Cumulative Incidence

Median of 3 years – very low certainty of evidence suggests that patients in the SpaceOAR™ +RT group at any time point during the study period were 64% less likely to present grade 1 urinary toxicity (HR 0.36, 95% CI 0.12 to 1.1; p=.046; participants = 140; see Figure 5-3 C) but the risk of having grade ≥2 urinary toxicity in the RT group was 22% lower (HR 1.22, 95% CI 0.40 to 3.72; p=.7; participants = 140; Figure 5-3 D). The differences between SpaceOAR™ +RT and the RT group for grades 1 and ≥2 late urinary toxicity were not statistically significant (null value of 1 lies in the 95% CI).

Figure 5-3: Cumulative incidence grade 1 and ≥2 urinary toxicity



Source: Hamstra [6] (licensed under CC BY-NC-ND 4.0)

Table 5-7 presents a high-level summary of findings reported for rectal and urinary toxicity in the included studies.The important results are the more severe adverse events (grades 3 and 4) and those that are longer term (i.e. after 3 to 6 months and the data after 3 years of follow-up).

Table 5-7: High-level summary of findings for rectal and urinary toxicity

Severity of toxicity/Duration of toxicity	Severity grade 1, 2	Severity grade 3 + 4
Short-term toxicity: i.e. up to 3 months	Less important	Important
Rectal (RCT)	>NS, >NS	>*, [?]
Rectal (nRCT)**	<<NS, [?]	[?], [?]
Urinary (RCT)	<NS, >NS	[?], [?]
Genitourinary (nRCT)	[?], <>NS,	[?], [?]
Long-term toxicity: i.e. 15 months	Important	Most important
Rectal 15 month (RCT)	>NS, >NS	>*, [?]
Urinary 15 months (RCT)	>NS, <NS	[?], [?]
3 years		
Rectal 3 years (RCT)	>SS, >[?]	>*, [?]
Urinary 3 years (RCT)	>NS, <NS	[?], [?]

*a single grade 3 case reported in the control group; **gel and balloon interventions
[?] = not reported, > intervention more favorable, < intervention less favorable, NS no significant differences between groups, SS significant differences between groups

Rectal Dose
This outcome was described as one of the primary endpoints. The proportion of patients achieving >25% reduction in rectal volume (i.e. rV70) due to spacer placement reached 97.3%. The mean SpaceOAR™+RT and RT group rV70 at baseline were 12.4% and 12.4% (p=.95) respectively. In the post-procedure treatment plans, they were 3.3% and 11.7% (p<.0001) respectively. The authors selected rV70 or greater due to its correlation with the risk of late gastrointestinal toxicity.

Table 5-8: Mean ± SD SpaceOAR™+RT group rectal dose volume baseline to post-spacer dose plans (Mariados 2015)

	rV70	**rV80**
% before SpaceOAR™+RT	12.4±5.4	4.6±3.1
% after SpaceOAR™+RT	3.3±3.2	0.6±0.9
% absolute reduction	9.07	3.93
% of relative reduction	73.3	86.3
p value	<.0001	<.0001

rV= rectal volume dose (70/80 Gy); RT: radiotherapy

Very low certainty of evidence in Wolf's study [9] showed that, when compared to the RT group, SpaceOAR™ or balloon+RT reduced dose to the rectum. The balloon spacer may be superior in reducing rectum dose but exhibited an average volume loss of >50% during the full course of treatment of 37–40 fractions, while the volume of SpaceOAR™ remained constant.

The surface that received the 95% isodose was 17.6 cm^2 for the control group, 10.9 cm^2 for the SpaceOAR™ +RT group (38% less than control) and 6.6 cm^2 for the balloon+RT group (63% less than control). The surface that received 85% isodose was 24.1 cm^2 for the RT group, 18.3 cm^2 for the SpaceOAR™ +RT group (24% less than control) and 13.2 cm^2 (42% less than control) for the balloon+RT group; the surface that received 60% isodose was 38.3 cm^2 in the RT group, 34.4 cm^2 in the SpaceOAR™ +RT group (10% less than control) and 29.7 cm^2 in the balloon+RT group (22% less than control) (See Table 5-9).

Table 5-9: Rectum surface mean value [9]

	Absolute dose (cGy) and Relative Dose (%)*					
	175.8 cGy 95%	**Dose reduction (%)**	**157.3 cGy 85%**	**Interv vs control (%)**	**111 cGy 60%**	**Interv vs control (%)**
Control cm^2. SD	17.6±8.3		24.1±9.3		38.3±12.2	
SpaceOAR™ +RT, cm^2. SD	10.9±8.8	38% less	18.3±11.1	24.1% less	13.2±10	10.2% less
Balloon+RT cm^2. SD	6.5±6.9	63% less	13.2±10	45.2% less	29.7±13.9	22.5% less

cGy: centigray (1 Gray equals 100 centigray); RT: radiotherapy; SD: standard deviation;

Distance between rectum and prostate – 3 months ± 1 week *[4]*
Low certainty of evidence in the RCT reported distance between rectum and prostate at 3-months follow-up.

Mean perirectal distance* SpaceOAR™ group

Pre-treatment	After insertion	3-months follow-up
1.6 ±2,2 mm	12.6±3.9 mm	9.0±5.9 mm

*distance between the posterior prostate capsule and anterior rectal wall on axial mid-gland T2 weighted MRIs

PSA relapse [4]
Low certainty of evidence from the RCT reported on PSA values pre-treatment and at 12 and 15 months post radiotherapy. The authors did not report standard deviations, and the information was not available from the authors or the manufacturer. Accordingly, no further calculations were possible.

	Pre-treatment	12 months	15 months
SpaceOAR™+RT	5.6 ng/mL	1.257 ng/mL n=148	1.135 ng/mL n=148
RT group	5.7 ng/mL	1.073 ng/mL n=71	1.073 ng/mL n=71
p value	.813	.968	.787

Ng/ml: nanograms per millilitre of blood; RT: radiotherapy

Health-related QoL

[D0012] – What is the effect of biodegradable rectum spacers on generic health-related QoL?

Only the RCT measured QoL,data for this outcome are presented in Mariados, Pieczonka and Hamstra [4, 6, 7].

QoL was assessed by the Expanded Prostate Cancer Index Composite (EPIC - 50 item), in which higher scores mean improvement in QoL. EPIC assesses the disease-specific aspects of prostate cancer and its therapies and comprises four summary domains: urinary, bowel, sexual and vitality/hormonal [13]. Data for vitality/hormonal domain was not reported.

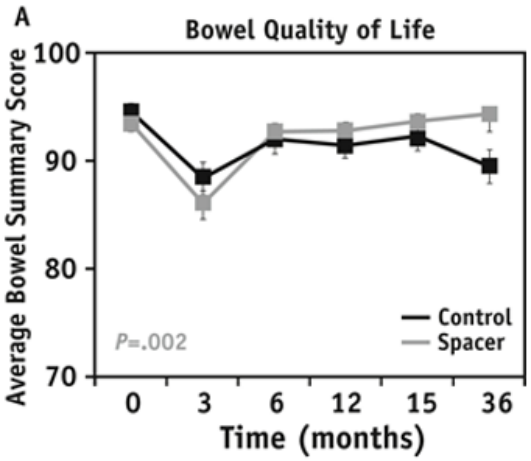
The EPIC questionnaire does not have an overall QoL summary, however, men experiencing minimal important differences (declines) in all 3 QoL summary domains at 36 months were 2.5% in SpaceOAR™ +RT vs 20% in RT (p=.002; difference relative to RT 88%) [12]. We therefore report results for this outcome in the disease-specific QoL section below.

[D0013] – What is the effect of biodegradable rectum spacers on disease-specific QoL?

Bowel, Urinary and Sexual QoL assessed using EPIC questionnaire

Very low certainty of evidence suggests there was a difference between groups over the entire follow-up time in bowel QoL (p=.002) See Figure 5-4. The evidence suggests that the mean difference of 5.8 points in the summary score met the threshold for MID of 4 to 6 points at 36 months (p<.05).

Figure 5-4: Bowel QoL EPIC Summary Score.



Source: Hamstra [6] (licensed under CC BY-NC-ND 4.0)

Bowel scores are presented for 3, 6, 15, 15 and 36 months according to the EPIC scale minimal clinical difference of 5 points or 2x -10 points declines [6, 7] (see Table 5-10 below).

3 months – Low certainty of evidence suggests that “mean changes in bowel and urinary QoL for the SpaceOAR™ +RT (-7.5 and -11.5) and control groups (-6.2 and-11.2) respectively were not significant”. The RT group had 5 fewer participants who experienced 5 point (RD 0.05, 95% CI -0.09 to 0.19) and 2 fewer participants who experienced 10-point declines (RD 0.02, 95% CI -0.11 to 0.15) compared to SpaceOAR™ +RT. Results are not statistically significant (null value of 0 lies in the 95% CI).

6 and 12 months – Low certainty of evidence suggests there were 8 fewer patients in the SpaceOAR™ group who experienced 5-point declines (RD -0.08, 95% CI -0.20 to 0.05) and 7 fewer who experienced 10-point declines (RD -0.07, 95% CI -0.17 to 0.04) at 6 months. At 12 months, there were 10 fewer cases of individuals in the SpaceOAR™ vs the RT group who experienced 5-point declines (RD -0.10, 95% CI -0.23 to 0.03) and 5 fewer cases who experienced 10-point declines (RD -0.05, 95% CI -0.15 to 0.06) in bowel QoL. Results are not statistically significant (null value of 0 lies in the 95% CI).

15 months – Low certainty of evidence shows there were 9 fewer cases of 5-point declines in the SpaceOAR™ +RT vs the RT group (RD -0.09, 95% CI -0.22 to 0.04) and also 9 fewer cases of individuals in the SpaceOAR™ +RT group who experienced 10-point declines (RD -0.09,95% CI -0.20 to 0.01) in bowel QoL. Results are not statistically significant (null value of 0 lies in the 95% CI).

Median of 3 years – Very low certainty of evidence suggests the SpaceOAR™ +RT group participants were less likely than the RT group to have either a 5-point (OR 0.28 or 72% increase in the odds, 95% CI 0.13 to 0.63; participants = 140) or 10-point decline (OR 0.30 or 70% increase in the odds, 95% CI 0.11 to 0.83; participants =140): the differences relative to the control group were statistically significant (null value of 1 does not lie in the 95% CI).

Table 5-10: Bowel QoL (EPIC questionnaire)

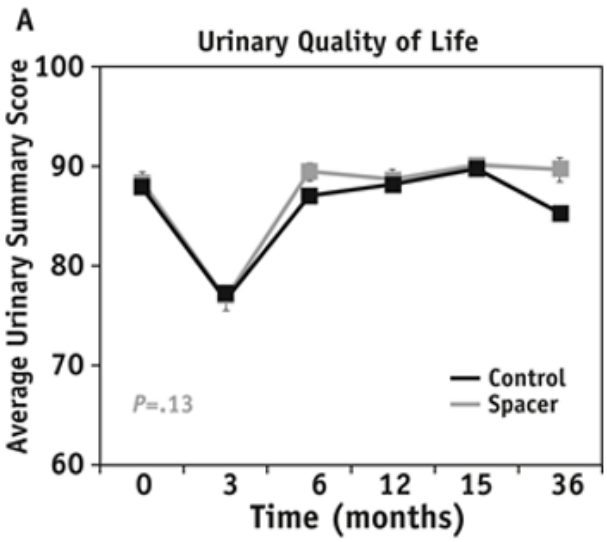
Bowel QoL	SpaceOAR™ Hydrogel	Control	% Difference	Effect size, 95% CI
Minimal Clinical Difference – 5 point				
3 months	73 (49.0%)	32 (45.7%)	<3.3%	RD 0.05, 95% CI -0.09 to 0.19
6 months	36 (24.3%)	23 (32%)	>7.6%	RD -0.08, 95% CI -0.20 to 0.05
12 months	35 (23.8%)	24 (33.3%)	>9.5%	RD -0.10, 95% CI -0.23 to 0.03
15 months	36 (24.5%)	24 (34.3%)	>9.8	RD -0.09, 95% CI -0.22 to 0.04
36 months	13 (14%)	19 (41%)	>27%	OR 0.28, 95% CI 0.13 to 0.63*
Minimal Clinical Difference x 2 – 10 point				
3 months	50 (33.6%)	23 (32.9%)	<0.7	RD 0.02, 95% CI -0.11 to 0.15
6 months	19 (12.8%)	14 (19.4%)	>6.3	RD -0.07, 95% CI -0.17 to 0.04
12 months	22 (15.0%)	14 (19.4%)	>4.4	RD -0.05, 95% CI -0.15 to 0.06
15 months	17 (11.6%)	15 (21.4%)	>9.8	RD -0.09,95% CI -0.20 to 0.01
36 months	5 (5%)	7 (21%)	>16%	OR 0.30, 95% CI 0.11 to 0.83*

Some data provided by Boston Scientific; > intervention more favourable, < intervention less favourable; CI: Confidence Interval; EPIC: Expanded Prostate Cancer Index Composite; OR: odds ratio; RD: risk difference
* statistically significant

Urinary QoL

Low to very low certainty evidence suggests no difference between groups over the entire follow-up time in urinary QoL (p=.13). See Figure 5-5.

Figure 5-5: Urinary QoL EPIC Summary Score



Source: Hamstra [6] (licensed under CC BY-NC-ND 4.0)

Urinary QoL scores are presented for 3, 6, 15, 15 and 36 months according to the EPIC scale minimal clinical difference of 5 points or 2x -10 points (see Table 5-11 below).

3 months – Low certainty of evidence suggests that “mean changes in bowel and urinary quality of life for the SpaceOAR™ +RT (-7.5 and -11.5) and RT groups (-6.2 and-11.2) were not significant”. There were 7 fewer patients in the RT groups who experienced 6-point declines (RD 0.07, 95% CI -0.07 to 0.21) and equal number of patients between groups who experienced 10-

point declines (RD 0.00, 95% CI -0.14 to 0.14) in urinary QoL. Results are not statistically significant (null value of 0 lies in the 95% CI).

6 and 12 months – Low certainty of evidence suggests there were 14 fewer participants in the SpaceOAR™ +RT group vs the control group who experienced 6-point declines (RD -0.14, 95% CI -0.26 to -0.01) and 13 fewer individuals who experienced 12-point declines (RD -0.13, 95% CI -0.24 to -0.03) at 6 months. There were similar number of cases in the SpaceOAR™ +RT and the RT groups who experienced 6-point (RD 0.00, 95% CI -0.12 to 0.12) and 12-point declines (RD -0.01, 95% CI -0.11 to 0.09) in urinary QoL at 12-months follow-up. Results are statistically significant (null value of 0 does not lie in the 95% CI) at 6 months, but not statistically significant at 12 months follow-up (null value of 0 lies in the 95% CI).

15 months – Low certainty of evidence shows there were similar numbers of patients in the SpaceOAR™ +RT and the control groups who experienced 6-point (RD 0.01, 95% CI -0.11 to 0.12) and 12-point declines (RD -0.03, 95% CI -0.12 to 0.06) in urinary QoL at 15 months follow-up. Results are not statistically significant (null value of 0 lies in the 95% CI).

36 months – Very low certainty of evidence suggests the SpaceOAR™ +RT group participants were less likely than the control to have either a 6-point (OR 0.41 or 59% increase in the odds, 95% CI 0.18 to 0.95; participants = 140) or 12-point decline (OR 0.31 or 69% increase in the odds, 95% CI 0.11 to 0.85; participants =140); the difference relative to the control group was statistically significant (null value of 1 does not lie in the 95% CI).

Table 5-11: Urinary QoL (EPIC questionnaire)

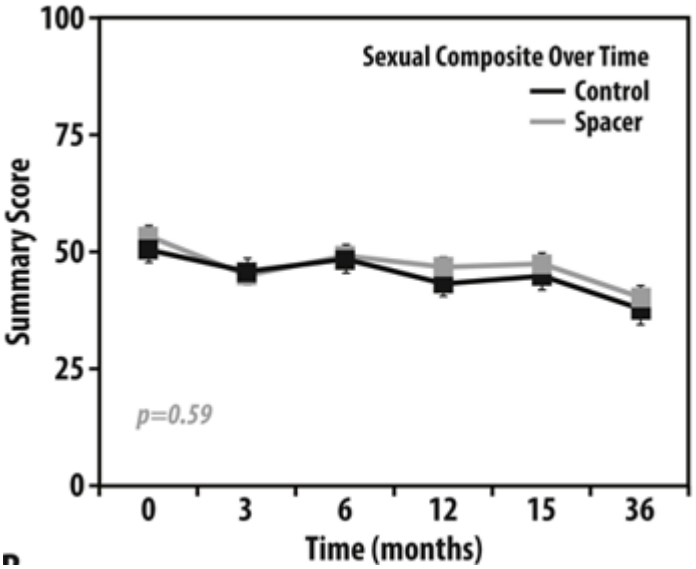
Urinary	SpaceOAR™ Hydrogel	Control	Difference	Effect size, 95% CI
Minimal Clinical Difference - 6 point				
3 months	97 (65.1%)	42 (60.0%)	<5.1%	RD 0.07, 95% CI -0.07 to 0.21
6 months	25 (16.9%)	22 (30.6%)	>13.7%*	RD -0.14, 95% CI -0.26 to -0.01*
12 months	37 (25.2%)	18 (25%)	<0.2%	RD 0.00, 95% CI -0.12 to 0.12
15 months	32 (21.8%)	15 (21.4%)	<0.4%	RD 0.01, 95% CI -0.11 to 0.12
36 months	28 (30%)	8 (17%)	>13%	OR 0.41, 95% CI 0.18 to 0.95*
Minimal Clinical Difference x 2-12 point				
3 months	70 (47.0%)	34 (48.6%)	<1.6%	RD 0.00, 95% CI -0.14 to 0.14
6 months	13 (8.8%)	16 (22.2%)	>13.4%	RD -0.13, 95% CI -0.24 to -0.03*
12 months	19 (12.9%)	10 (13.9%)	>1%	RD -0.01, 95% CI -0.11 to 0.09
15 months	14 (9.5%)	9 (12.9%)	>3,4%	RD -0.03, 95% CI -0.12 to 0.06
36 months	22 (23%)	4(8%)	>15%	OR 0.31, 95% CI 0.11 to 0.85*

Some data provided by Boston Scientific; > intervention more favorable, < intervention less favourable; CI: Confidence Interval; EPIC: Expanded Prostate Cancer Index Composite; OR odds ratio.* statisticaly significant results; RD: risk difference

Sexual QoL

Very low certainty of evidence suggests sexual function was similar in both groups over the entire follow-up time between groups (p=.6) (see Figure 5-6); there were no differences in the proportion of patients with MID changes.

Figure 5-6: Sexual QoL EPIC Summary Score



Source: Hamstra [6] (licensed under CC BY-NC-ND 4.0)

Satisfaction

[D0017] – Were patients satisfied with biodegradable rectum spacers?

The studies did not measure this outcome and we were unable to answer this research question.

Resource use – procedural time

Urologists and oncologists rated SpaceOAR™ application as 'easy' and 'very easy' 98.7% of the time [4] which may imply short procedural times. The trial also showed that physicians placing hydrogels found the procedure to be straightforward and achieved a very high placement success rate [25]. There was no information about resource use or procedural time in the nRCT.

6 SAFETY (SAF)

6.1 Research questions

Element ID	Research question
[C0008]	How safe are biodegradable rectum spacers in addition to radiotherapy?
[C0002]	Are the harms related to dosage or frequency of using biodegradable rectum spacers?
[C0004]	How does the frequency or severity of harms change over time or in different settings?
[C0005]	Which susceptible patient groups are more likely to be harmed by the use of rectum spacers?
[B0010]	What kind of data/records and/or registry is needed to monitor the use of biodegradable rectum spacers in addition to radiotherapy and/or other therapies?

6.2 Results

Included studies

Only the RCT (Mariados 2015 and some companion studies) reported on the safety of the technology.

Patient safety

[C0008] – How safe is the technology in relation to the comparator(s)?

Death related to adverse events

There were no deaths related to the technology reported in these studies.

Severe to life-threatening adverse events (grades 3 to 4)

There were no life-threatening adverse events related to the technology.

Mild to moderate adverse events (grades 1 to 2)

Procedural adverse events were scored as definitely, possibly, unlikely, or definitively not related to the procedure. Only those scored by the blinded adjudicating panel as definitely or possibly were included as adverse events (information provided by Dr Hamstra). Low certainty of the evidence for procedure-related adverse events was reported in Mariados [4] and companion studies [7, 12, 25] as follows; [C0008]

- There were no unanticipated SpaceOAR™ Hydrogel related adverse events; mild transient procedural adverse events (perineal discomfort and others) were noted in 10% of the spacer patients; the CEC blinded adjucidation committee of all recorded adverse events found no spacer related adverse events (Mariados 2015);
- Grade 1 events requiring no medication were - (1 each) - hematospermia, anorectal pressure, hematuria, tight pain, discomfort while sitting, perineal pain, rectal pain, rectal bleeding (attributed to preoperative enema), constipation and flatulence;
- Grade 2 transient events treated with medication included mild lower urinary tract symptoms and hypotension, and moderate perineal pain. There were no implant infections, rectal wall ulcerations or other more serious complications (Pieczonka 2015);

- procedural rectal wall infiltration was seen in 9 (6%) SpaceOAR™ Hydrogel patients with scores of 1 (n=5, 3.4%), 2 (n=3, 2%), and 3 (n=1, 0.7%) respectively (Fisher-Valuck and Karsh 2017) (See Table 6.1).
- 2/149 spacer patients had no SpaceOAR™ Hydrogel present after application: hydrogel injected beyond the prostate in 1 patient, no hydrogel injected in the other due to inadvertent needle penetration of the rectal wall requiring study mandated termination of the procedure. (Karsh 2017)

The same oncologist assessed the extent of hydrogel rectal wall infiltration (RWI) for each patient by evaluating every axial slice, and scoring using a qualitative method. Scoring ranged from no RWI (0) to minimal (1, small discrete areas), moderate (2, <25% of rectum circumference), and significant (3, ≥25% of rectum circumference) infiltration. The table below shows procedural adverse events.

Table 6-1: Rectal wall infiltration (RWI) (adverse events)

Procedural adverse events	
RWI	**No. of Patients (%)**
0	140 (94)
1	5 (3.4)
2	3 (2)
3	1 (0.7)

Any adverse events

[C0002] – **Are the harms related to dosage or frequency of using/inserting a biodegradable rectum spacers?**

There were no device-related adverse events, rectal perforations, serious bleeding or infections in either group.

[C0004] – How does the frequency or severity of harms change over time or in different settings?

We did not identify evidence to answer the research question on the change in frequency or severity of harms over time or in different settings.

[C0005] – Which susceptible patient groups are more likely to be harmed by the use of biodegradable rectum spacers?

We did not identify evidence to answer this research question.

[B0010] – What kind of data/records and/or registry is needed to monitor the use of biodegradable rectum spacers in addition to radiotherapy and/or other therapies?

It would be important for information on the effectiveness and safety of biodegradable rectum spacers to be collected in cancer registries for future analysis. Registries play an important role in improving health outcomes. Through the use of such registries, health-care providers can compare, identify, and adopt best practices for patients with prostate cancer. This offers the ability to effectively identify and manage patients with a particular condition and improve coordination of care.

Table 6-2: Frequency and severity of grade 3-5 adverse events.

Details for each study are available in evidence tables included in Appendix 1.

System organ/class/adverse events	Grade 3-5		
	Spacer +RT	RT alone	
Adverse events grades 3-4, and death related to adverse events, grade 5	There were no grade 3-4 adverse events or grade 5 (death) adverse events reported in these studies		

Abbreviations: CI, confidence interval

Table 6-3: Frequency and severity of grade 1-2 adverse events in one RCT [4].

System organ/class/adverse events	Grade 1-2
	SpaceOAR™ Hydrogel (n=148)
Procedural adverse events	There were no unanticipated SpaceOAR™ Hydrogel related adverse events; mild transient procedural adverse events (perineal discomfort and others) were noted in 10% of the spacer patients; the CEC blinded adjudication of all recorded adverse events found no spacer-related adverse events (Mariados 2015);
	Grade 1 events requiring no medication were - (1 each) - hematospermia, anorectal pressure, hematuria, tight pain, discomfort while sitting, perineal pain, rectal pain, rectal bleeding (attributed to preoperative enema), constipation and flatulence; Grade 2 transient events treated with medication included mild lower urinary tract symptoms and hypotension, and moderate perineal pain. There were no implant infections, rectal wall ulcerations or other more serious complications (Pieczonka 2015);
	Procedural rectal wall infiltration was seen in 9 (6%) SpaceOAR™ Hydrogel patients with scores of 1 (n=5, 3.4%), 2 (n=3, 2%), and 3 (n=1, 0.7%) respectively (Fisher-Valuck and Karsh 2017)
	2/149 spacer patients had no SpaceOAR™ Hydrogel present after application: hydrogel injected beyond the prostate in 1 patient, no hydrogel injected in the other due to inadvertent needle penetration of the rectal wall requiring study-mandated termination of the procedure. (Karsh 2017)

7 POTENTIAL ETHICAL, ORGANIZATIONAL, PATIENT AND SOCIAL, AND LEGAL ASPECTS (ETH, ORG, SOC, LEG)

Appendix 3 contains the completed checklist for potential ethical, organizational, patient and social, and legal aspects. To answer the checklist we used information from the literature search, from web-searches and from the clinical experts as information sources.

The checklist indicates that there might be ethical, organizational and legal aspects that the users of this assessment report might wish to evaluate further. It was not our objective to provide an in-depth overview of each aspect.

8 DISCUSSION

The HTA included 2 studies involving 298 participants and 2 different biodegradable spacers (SpaceOAR™ Hydrogel and ProSpace™ balloon) intended to achieve a reduction in rectal dose to the rectum during prostate cancer radiotherapy. The participants' characteristics were reported in one of the studies (RCT); they were 85% Caucasian, age ~67 years, with T1 and T2 localized prostate cancer, Gleason 49-36%, prostate volume 50-47ml and were undergoing IG-IMRT radiotherapy.

Findings related to the health problem and the technology

AUA/ASTRO/SUO Guideline [102, 103] suggests that, in most cases, there is not a single best treatment choice with regard to oncological outcomes or side effects. Management of prostate cancer requires a tailored and personalized approach. Each treatment has different side effects, impacting the QoL of patients and their families. Therefore, among treatment options, men should be offered the opportunity to consult with both a urologist and a radiation oncologist [104]. Clinicians should fully engage in shared decision making, allowing patient values to drive this decision.

Radiotherapy is a well-established curative treatment method for prostate cancer with known associated risk of rectal toxicity associated with high local doses [105]. The use of a biodegradable rectum spacer is presented as an option for patients who choose to treat their prostate cancer with radiotherapy as a curative treatment. At least three manufacturers provide CE-approved devices in Europe. These manufacturers claim the following benefits can be attributable to biodegradable rectum spacers: minimize radiotherapy toxicity to the anterior rectal wall; increase the distance between prostate and rectum; protect QoL; increase likelihood of maintaining sexual function; better urinary and bowel QoL; fewer longer-term side effects. Chapter 3 provides a description of the technical characteristics of this technology. Results of this HTA however, can only confirm few of the benefits clamied by manufactures.

Biodegradable materials evaluated for use as rectum spacers in this report, including polyethylene glycol hydrogels and saline-filled balloons, showed little or no difference in rectal or urinary toxicity at short (3 months) and long-term (15 months) follow-up. Very low certainty of evidence at a median of 3 years suggests SpaceOAR™ +RT may reduce rectal toxicity grade 1. It is possible that the performance of these devices may differ according to radiotherapy protocols or patient characteristics which this report was unable to analyse. Longer than 3 years' follow-up may show different results, although attributing results to the spacer at longer follow-up times may prove difficult.

Biodegradable rectal spacers are approved for use in Europe so implementation is left to the discretion of individual countries. It is envisaged that each country may consider their local operational environment and professionals available in facilitating the adoption of this technology. For example, the latest HAS report [106] suggests the implantation of the spacer should be carried out by a doctor belonging to one of the following specialties: interventional radiologist; oncologist-radiotherapist or urologist. Centres with brachytherapy services may choose to adapt their system to allow for the transperineal insertion of the rectal spacer within the radiotherapy department, whereas those without brachytherapy services may choose to engage their local (interventional) radiology or urology departments. The associated costs (not assessed here) 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 [19]. There are few recent cost-effectiveness analyses in the literature including SpaceOAR™ containing uncertainty and suggesting more evidence is currently needed for decision making. [107, 108].

Effectiveness and safety findings

We selected rectal and urinary toxicity, overall QoL, bowel, urinary and sexual QoL, and reduction in rectal dose as critical outcomes for this assessment. Other important outcomes were increased distance between prostate-rectum, overall survival, and PSA. We included technology-related

adverse events grades 1 to 5. We considered adverse events 3 to 5 as critical, and grades 1-2 as important. Overall survival was not measured in the studies.

The relationship between dose and toxicity to the rectum parameters is one that has proven to be challenging. As seen in this assessment, spacers do reduce rectal radiation exposure, but it is unclear whether this impacts rectal toxicity and QoL. It is also uncertain when and how is best to measure these important outcomes for patients. Our assessment found low to very low certainty evidence suggesting that transperineal biodegradable spacers (SpaceOAR™ and balloon) for men undergoing radiotherapy for localized prostate cancer may make little or no difference to acute and late rectal and urinary toxicity. Our results are similar to Forero [27] who reported that, whereas there was evidence that SpaceOAR™+RT use does result in lower rectal radiation exposure, this may not contribute to an important reduction in rectal toxicity; the author based this conclusion upon reviewing one RCT and three observational studies. In this assessment, the RCT measured rectal and urinary toxicity at 15 months, and a median of 3 years when the sample loss to follow-up was higher than 20%; this loss to follow-up posses a serious threat to the validity of the results [109].

Injecting an absorbable hydrogel or balloon spacer appears to be associated with decreased rectal dose. We can argue that the toxicity results may differ if the population characteristics were to change. For example, the reduction may have particular utility in previously irradiated patients [110]. The literature indicates individuals with particular risk factors may benefit from biodegradable spacers. Vanneste's case report [111] describes the use of a biodegradable balloon implant to protect the rectum during prostate cancer radiotherapy for a patient with active Crohn's disease. This patient was at high-risk for rectal toxicity and was successfully irradiated to his prostate with only a grade 1 urinary toxicity, no acute rectal toxicity or toxicity flare of the IBD.

The insertion of SpaceOAR™ or balloon was acceptable and regarded as an easy procedure and achieved a prostate-rectum distance of approximately 1.2 cm [4]. The literature presents different distances created by the different biodegradable spacers. For example, a recent systematic review analysis of five studies [23] reported a weighted mean perirectal separation distance of 1.12cm (95% CI 1.01 to 1.23 cm) while Ho and colleagues reported an average peri-rectal spacing of 0.75 ± 2.6 cm using SpaceOAR™ hydrogel [112]. An earlier study by Wilder and colleagues [113] reported the use of HA in 35 patients who underwent high-dose-rate brachytherapy. HA increased the separation between the prostate and rectum by 0.6-1.9cm (media 1.3cm). In contrast, Thomas and colleagues [114] present a prospective review of the safety and efficacy of insertion of BioProtect balloon prior to prostate radiotherapy. Evaluation MRI imaging of the balloons was performed 24 hours post-implant and showed a mean separation of rectum and prostate of 2.1cm (range 1.7 to 2.5cm). Costa [115] suggests the BioProtect balloon spacer may be advantageous compared with other rectum spacers, in particular due to the amount of spacing achieved and the possibility of adjustable placement (including deflation and repositioning) during the procedure, allowing for optimal spacing.

Our results showed better bowel QoL but no difference for Sexual or Urinary QoL over the entire follow-up period. The literature report similar results for bowel QoL. Eade [116] reported QoL at 2 years following IMRT and hydrogel for prostate cancer; authors shown that 2-year bowel QOL was unchanged in patients with hydrogel, despite delivered doses in excess of 80 Gy. A study by Pinkawa [45] reported the first five-year QoL results in a group of prostate cancer patients. QoL was measured by the EPIC-50 items scale, patients were treated with IMRT and a hydrogel spacer. Mean bowel function and bother score changes of >5 points in comparison to baseline levels before treatment were found only at the end of RT (10-15 points; $p < .01$) for patients treated with a hydrogel spacer. Further, a study by Seymour [117] presents a pooled analysis of a prospective cohorts with long-term follow-up (median 39 months) QoLdata (EPIC) with or without hydrogel spacers. After prostate radiotherapy with up to 5 years of follow-up, utilization of a hydrogel spacer was associated with preservation of bowel QoL.

While injury to the rectal wall is possible during RT, data in this HTA does not support the use of an invasive procedure like a biodegradable spacer for urinary and sexual quality of life.

Safety

Balancing benefits against its potential harms is a complex task. Biodegradable rectum spacers safety cannot be considered an absolute; it can only be assessed relative to their benefits. Biodegradable rectum spacers are a technology in early phases following the time of marketing; the amount of information on benefits and risks, especially long term, is relatively small, and often based on highly selected populations (i.e. age, comorbidities, use of concomitant medications, and other factors) requiring judgement from the practitioner involved. Evaluation of safety may require collaborative interactions among regulatory bodies, health authorities, and manufactures for detecting, interpreting and reporting adverse events, especially long term. This will provide information that will allow physicians and patients to make educated decisions about the potential benefits and harms of biodegradable rectum spacers.

For the safety domain, we have low certainty evidence from one RCT and companion studies, which prevents us from fully understanding this important outcome. That means we have very little confidence in the results and that the true effect is likely to be substantially different from the results from the studies included. It is also important to note that safety, in general, is reported too inconsistently in studies to allow cross-comparisons. Some of the study authors in the RCT have received support and honoraria from the industry. Such financial relationships are a general topic of concern that can bias results [118].

Other procedural adverse events for the technology have been documented in the literature. For example, we found several reports in the United States Manufacturer and User Facility Device Experience (MAUDE) database for the SpaceOAR™ Hydrogel. [119]. The numbers of SpaceOAR™ reports in MAUDE has been discussed in the literature. A recent publication [120] suggests there were 22 unique reports discussing 25 patient cases in the MAUDE database from January 2015 to March 2019, with an increasing number of reports each year up to 2018. Authors mentioned reported complications include acute pulmonary embolism, severe anaphylaxis, prostatic abscess and sepsis, purulent perineal drainage, rectal wall erosion, and rectourethral fistula. In response to the above, a recent editorial suggests that the number of medical device reports in MAUDE has indeed increased, but the authors emphasized this increase is normal and proportionate to device usage and the rate of reports has remained relatively constant over time, ranging from 0.3 to 0.6 per 1000 SpaceOAR™ cases performed [121].

Other procedural adverse events reported for the hydrogel technology are a rectal ulcer after hydrogel injection [122, 123], and rectal necrosis following **i**nadvertent rectal wall injection (with hydrogel) resulting in focal rectal mucosal necrosis and bladder perforation [124]. Infections were mentioned in a case series of 200 patients; this is a natural consequence of inserting the spacer in the transperineal space. In the case series, the patients reported bacterial peritonitis and bacterial epididymitis in those injected with a hydrogel spacer. The bacterial peritonitis occurred after prostate biopsies. No infections were reported in the patients treated with HDR brachytherapy without hydrogel [125].

With regard to the balloon adverse events, one case series of 27 patients reports the following: penile bleeding and acute urinary retention (needed catheterisation, which resolved within a few hours) during balloon insertion [126], dysuria and nocturia (grade 1-2) were also reported during balloon insertion and during radiotherapy. Other events reported during radiotherapy in the same case series included diarrhoea, mild proctitis, and blood in the faeces, constipation, erectile dysfunction, itching, fatigue and decreased urine flow [126].

In agreement with other literature, we found it is advisable that the transperineal placement procedure be performed by trained personal (i.e. radiation oncologist, urologist or interventional radiologist with experience in transperineal procedures and transrectal ultrasonography) [23]. More procedural “mistakes” may be seen at the beginning of a trial and decrease as the health personnel gain experience with the technique.

Evidence gaps

There were 2 trials meeting our PICO and inclusion criteria; this is clear evidence that this type of intervention needs to be tested with prospective comparative designs in the future. The small number of prospective studies with a comparator we have included makes it impossible to answer the research questions for all patients with prostate cancer.

Only the RCT included information on characteristics of the participants (age, race, and stage tumours, prostate volume) which limits the generalizability of results; these studies used the same radiotherapy technique, but only the RCT presented long-term results with a follow-up at 3 years. This implies that the presented data might be an underestimate.

At the individual level, one study evaluated SpaceOAR™ in individuals at stage T1 and T2 (information on the RCT), but who will benefit most from the intervention is still unclear. In this regard, Vanneste [127] developd a decision rule based on clinical risk factors to select those patients who are expected to benefit most from spacer implantation. There is a need to include advanced stages (T3) in future trials, and those with particular characteristics important to patients like inflammatory bowel disease and higher prostate volume. Other patient comorbidities, like diabetes or anticoagulant medication consumption at the start of the trial, will be interesting to explore.

The reporting on biodegradable rectum spacer outcomes important to this team derives from two small studies with high risk of biases. Notable areas of inadequate reporting were study methods (measuring and reporting adverse events, a key feature of the intervention). Blinding of participants to their group assignment or study hypothesis (or both) is very important, and we recommend that researchers report this information in detail in future trials. This will help increase the robustness of future reviews on this topic.

More details with respect to the procedure adverse events or adverse events related to the spacer itself are needed to better judge safety of the intervention. Monitoring methods were poorly or not documented in the included studies (we sought information from authors and manufacture). Reporting of procedural adverse events should focus on all treatment components and should cover both acute and late times. Future studies that better document these details can further our understanding of possible treatment-response relationships between spacer and radiotherapy outcomes.

We identified 15 trial registry records that include a biodegradable rectum spacer. Of these, n=3 are completed. The status of the remainder are n=3 “unknown”, n=1 “suspended”, n=3 “no longer recruiting”. On the other hand, there were n=2 “active, not recruiting” and n=3 “recruiting”. Appendix 1 Table A3 presents trial registry records found, including the population, intervention, comparator and main endpoints.

Relation to other assessments

Some previous synthesis work has drawn conclusions about the possible benefit of rectum spacers that are not consistent with our findings.

The NICE 2017 [20] overview included all types of biodegradable spacers (gel or hydrogel, hyaluronic acid, human collagen and biodegradable balloons) covering the period up to April 2017. The overview included several study designs and radiotherapy approaches not included in this assessment. It concluded that the evidence on the safety and efficacy of insertion of a biodegradable spacer to reduce rectal toxicity during radiotherapy for prostate cancer was adequate to support the use of this procedure, provided that standard arrangements are in place for clinical governance, consent and auditing. Similar to our findings, NICE further recommended the procedure should only be done by clinicians with training in, and experience of, transperineal interventional procedures. The development of NICE medical technology guidance on SpaceOAR™ was suspended in 2019 because, after development of the final scope, NICE determined that the topic was no longer suitable for medical technologies guidance. The topic will now be considered for selection by the technology appraisal programme.

The CADTH rapid response summary report [18] focused on SpaceOAR™. It concluded that SpaceOAR™ was 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 (patients with localized prostate cancer). The report includes the same RCT as this assessment, but the authors also included two systematic reviews, which reported no significant clinical benefits, and results were therefore uncertain. One systematic review developed for a health technology assessment did not recommend the routine use of SpaceOAR™ for prostate cancer, in consideration of the high costs for their patients. For patients receiving high-dose SBRT, the use of SpaceOAR™ was found to be cost-effective.

A recommendation report by Chung et al., on behalf of CCO [19], reviewed the NICE 2017 overview [20], a Cochrane review [128] and Forero HTA [27]. The authors included one RCT [4] and three nRCTs [98, 129, 130] and recommended biodegradable spacer insertion to be used to decrease toxicity and maintain QoL in appropriately selected prostate cancer patients receiving radiotherapy. The authors point out that, given the low rates of toxicity observed overall in both arms of the included RCT (the same as in this assessment), there may be limited benefit to routine application of this technology and that the appropriate selection of patients is warranted.

Two recent publications have focused on hydrogel spacers. The HAS 2020 [106] report focused on SpaceOAR™ only. It considers that, in the absence of an alternative available for the patients and taking into account the gravity of the consequences of radiotherapy, the intervention (hydrogel) is of public health interest. The report highlights that the indication is for prevention of rectal toxicity from EBRT with a curative aim for prostate cancer in patients at low or intermediate risk. Our results are in agreement with Miller's systematic review [23]. The review included 7 studies and found the insertion of a perirectal hydrogel spacer was associated with less rectal irradiation, decreased rectal toxicity and higher bowel QoL in the long term.

Limitations of this assessment

Through a review of the evidence, web searches, contacts with clinical experts and manufacturers, we identified three manufacturers that provide CE-approved devices in Europe. A public database of CE-approved systems is lacking and therefore we acknowledge that there may be additional CE approved biodegradable spacers available that we are not aware of.

We found an overwhelming number of single-arm studies, posters and abstracts including the technologies of interest. This may be a sign of perceived value or need for the technology, or the development of alternative (new to the market) biodegradable rectum spacers. It may also be an indication that there are difficulties or ethical concerns in conducting randomized controlled studies in this area. Due to the high number or records with the above characteristics, we were unable to contact authors, extract and analyze data as planned. We acknowledge that device-related safety results (or results as a whole) may have been different had we been able to consider that information.

In terms of the characteristics of the participants, only the RCT provided stage and age, prostate volume and PSA values. Benefits and harms of biodegradable spacers are limited to those individuals described in this RCT.

Whilst some important outcomes were reported, the included studies did not report data in a form that we could use in a meta-analysis (e.g. sexual QoL). Reporting data in percentages was a common feature of these studies. Safety outcomes were only reported in the RCT.

9 CONCLUSION

We included one RCT and one nRCT assessing the effectiveness of this technology. In addition, we found previous reports on biodegradable spacers to reduce rectal toxicity in prostate cancer radiotherapy, namely NICE (biodegradable spacers), CADTH (hydrogel), Chung (hydrogel), Forero (hydrogel), HAS (hydrogel) and a recently published systematic review (hydrogel).

Although biodegradable rectum spacers to reduce toxicity for prostate cancer look promising, single small studies provide low to very low evidential certainty. Furthermore, outcomes important to people with cancer, including bowel, urinary and sexual QoL, different patient characteristics (e.g. cancer stage and comorbidities), as well as long-term effects were not present in both included studies. The nature of the curative intervention (radiotherapy) requires large multi-centre controlled trials to establish whether biodegradable rectum spacers are effective.

The evidence in this report describes improvements in bowel QoL. The dose received by the rectum decreased in both studies but improvements in toxicity were seen at long term follow up only (very low certainty of evidence). The certainty of the evidence was rated as low and very low, meaning that further research is very likely to have an important impact. Adverse events were only reported in the RCT and not systematically. There were no Grade 3,4,or 5 device related adverse events. But there are more reports as these devices are used more often.

The claimed benefits of rectum spacers for prostate cancer cannot be confirmed or rejected with the currently available evidence. Further research is needed that evaluates the effects of biodegradable rectum spacers in various populations, with different radiotherapy techniques for curative disease, and including long follow-up times. The research should also focus on reporting on both acute and late adverse events in a more systematic manner. At the methodological level, future research should incorporate blinding for outcome assessors, improve reporting biases, and report clearly on any loss to follow-up and how these were handled.

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75 Years

Males

40 Interventional

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

DOCUMENTATION OF THE SEARCH STRATEGY

Search log - Biodegradable rectum spacers to reduce toxicity for prostate cancer
Search I: Systematic reviews and Health Technology Assessment (HTA)
Search date: 2019.10.02.-04.
Search II: Primary studies
Search date: 2019.11.11.-12.
Searched by: Ingrid Harboe, information specialist NIPHNO, Peer review: Gyri Synnøve Hval Straumann, information specialist NIPHNO
External review: IQWIG

Search I: Systematic reviews and HTA

Search I: Systematic reviews and HTA Search date: 2019.10.02.-04. Name of database	Hits	
	Systematic review; HTA; Guideline	Clinical trial; Register study; Planned, ongoing, completed studies
Cochrane Library: CDSR Reviews; Protocols	1 0	-
Cochrane Library: Trials (CENTRAL)	-	97
Centre for Reviews and Dissemination (NIHR) - HTA	4	-
Ovid MEDLINE	10	41
AMED (Ovid)	0	0
Embase (Ovid)	268	300
Epistemonikos	12	3
National Guideline Clearinghouse	0	-
Guidelines International Network (GIN)	0	-
HTAi Vortal* (Health Technology Assessment International). Hand search: CADTH; NICE; NIHR; AETSA; AHRQ; SBU;	3	-
Devices@FDA	0	-
Ongoing projects and trials		
Clinical Trials (US)	-	16
ICTRP (WHO)	-	9
PROSPERO	0	-
POP database	0	-
Total including duplicates	298	466
Total without duplicates	275	293

*The Vortal's search function has closed down. See table for searched sources. See INAHTA for agencies.

Search Strategy: Search I
Databases (federated search): **Embase** 1974 to 2019 October 01;
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to October 01, 2019
Search filter, study design:
Systematic review/ Health Technology Assessment line #22-#24 (Ovid/ adjusted Cochrane search filter)
Controlled and/or longitudinal studies line #30-#32 (Center for Evidence-Based Management)
Register studies (unpublished NIPHNO search filter line #38)

Searches
exp Prostatic Neoplasm/
prostate tumor/ [Embase]
(prostat* adj4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or lump* or masses* or sarcom* or metastas*)).ti,ab,kw.

or/1-3
Hydrogels/
hydrogel/ [Embase]
Hydrogel, Polyethylene Glycol Dimethacrylate/ or Polyethylene Glycols/ or Hyaluronic Acid/ or exp Collagen/
(hydrogel* or hydrodissect* or DuraSeal or (polyethylene adj3 glycol) or liquid-to-solid).ti,ab,kw.
(spacer* or spacing or spaceOAR or (separat* adj6 prostat* adj3 rect*) or ProSpace or ((biodegradable or bioresorbable) adj3 polymer) or (biodegradable adj3 balloon*) or ((hyaluconic adj3 acid*) or collagen)).ti,ab,kw.
((perirect* or rect* or prostate-rect* or denonvillier* or transperineal*) adj4 space*).ti,ab,kw.
or/5-10
4 and 11
limit 12 to yr="2010 -Current"
Animals/
Humans/
14 not (14 and 15)
(news or editorial or comment).pt. use ppezv
(letter or editorial or note).pt. use oemezd
conference abstract.pt. use oemezd
13 not (16 or 17 or 18 or 19)
remove duplicates from 20
limit 21 to "reviews (best balance of sensitivity and specificity)"
(meta-analysis or review).pt. or review literature as topic/ or technology assessment, biomedical/
((systematic* adj3 (review* or overview* or synthes*)) or meta-analys* or metaanalys* or technology assessment* or HTA).ti,ab,kw.
21 and (23 or 24)
22 or 25 [SR/HTA]
26 use ppezv
26 use oemezd
limit 21 to "therapy (best balance of sensitivity and specificity)"
((Randomized Controlled Trial or Controlled Clinical Trial).pt. or Clinical Trials as Topic/ or (randomized or randomised or phase 3 or phase iii).ti,ab. or randomly.ab. or placebo.ab. or trial.ti.) use ppezv
randomized controlled trial/ or crossover-procedure/ or double-blind procedure/ or single-blind procedure/ or (randomized or randomised or phase 3 or phase iii).ti,ab. or randomly.ab. or placebo.ab. or trial.ti. use oemezd
(experiment* or (controlled adj (stud* or trial or group)) or (control adj variable) or (comparison adj group) or (comparative adj stud*) or quasi or longitudinal or laboratory or (before and after stud*) or (pretest adj post*) or (time adj series) or (case adj (control or cohort)) or (cohort adj stud*) or

(prospective adj stud*)).ti,ab.
21 and (30 or 31 or 32)
29 or 33
34 use ppezv
34 use oemezd
(Registries/ or Medical Record Linkage/ or Medical records systems, computerized/) use ppezv or Register/ use oemezd
(((registry or registries or register or registers or database* or databank* or repositor*) adj3 multiplesclerosis) or (MS* adj (regist* or database or databank or repositor*)) or (regist* adj2 (stud* or data oranalys* or report*)) or register based or panel data or (cohort adj2 (prospective or longitudinal)) or longitudinaladj1 prospective or ((real world or real life) adj2 (data or evidence or stud* or result* or outcome*)) or ((real world or real life) adj5 (data* or evidence or research or registry or registries or registeror registers))).tw,kw,kf.
(((medical or patient) adj2 (register or registers or registry or registries)) or patient-relevant outcome*).tw,kw,kf.
21 and (37 or 38 or 39) [Reg.stud.]
40 use ppezv
40 use oemezd

Database: AMED (Allied and Complementary Medicine) 1985 to September 2019
exp Prostatic Neoplasms/
(prostat* adj4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or lump* or masses* or sarcom* or metastas*)).ti,ab,hw.
or/1-2
Hydrogels/
Hydrogel, Polyethylene Glycol Dimethacrylate/ or Polyethylene Glycols/ or Hyaluronic Acid/ or exp Collagen/
(hydrogel* or hydrodissect* or DuraSeal or (polyethylene adj3 glycol) or liquid-to-solid).ti,ab,hw.
(spacer* or spacing or spaceOAR or (separat* adj6 prostat* adj3 rect*) or ProSpace or ((biodegradable or bioresorbable) adj3 polymer) or (biodegradable adj3 balloon*) or ((hyaluconic adj3 acid*) or collagen)).ti,ab,hw.
((perirect* or rect* or prostate-rect* or denonvillier* or transperineal*) adj4 space*).ti,ab,hw.
Or/4-8
3 and 9
Limit 10 to yr="2010 -Current"
Animals/
Humans/
12 not (12 and 13)
(news or editorial or comment).pt.
(letter or editorial or note).pt.
Conference abstract.pt.
11 not (14 or 15 or 16 or 17)
(meta-analysis or review).pt. or review literature as topic/ or technology assessment, biomedical/
((systematic* adj3 (review* or overview* or synthes*)) or meta-analys* or metaanalys* or technology assessment* or HTA).ti,ab,hw.
18 and (19 or 20)
(experiment* or (controlled adj (stud* or trial or group)) or (control adj variable) or (comparison adj group) or (comparative adj stud*) or quasi or longitudinal or randomized or randomly or laboratory or (before and after stud*) or (pretest adj post*) or (time adj series) or (case adj (control or cohort)) or (cohort adj stud*) or (prospective adj stud*)).ti,ab.
(((registry or registries or register or registers or database* or databank* or repositor*) adj3 multiplesclerosis) or (MS* adj (regist* or database or databank or repositor*)) or (regist* adj2 (stud* or data oranalys* or report*)) or register based or panel data or (cohort adj2 (prospective or longitudinal)) or longitudinaladj1 prospective or ((real world or real life) adj2 (data or evidence or stud* or result* or outcome*)) or ((real world or real life) adj5 (data* or evidence or research or registry or registries or registeror registers))).ti,ab.
18 and (22 or 23)

Database: Cochrane Library
MeSH descriptor: [Prostatic Neoplasms] explode all trees
(prostat* near/4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or lump* or masses* or sarcom* or metastas*)):ti,ab,kw
#1 or #2
MeSH descriptor: [Hydrogels] explode all trees
MeSH descriptor: [Hydrogel, Polyethylene Glycol Dimethacrylate] this term only
MeSH descriptor: [Polyethylene Glycols] this term only
MeSH descriptor: [Hyaluronic Acid] explode all trees
MeSH descriptor: [Collagen] explode all trees
(hydrogel* or hydrodissect* or DuraSeal or (polyethylene near/3 glycol*) or liquid-to-solid):ti,ab,kw
(spacer* or spacing or spaceOAR or (separat* adj6 (prostat* adj3 rectum) or ProSpace or ((biodegradable or bioresorbable) adj3 polymer) or (biodegradable adj3 balloon*) or (hyaluconic adj3 acid*) or collagen):ti,ab,kw
((perirect* or rect* or prostate-rect* or denonvillier* or transperineal*) near/4 space*):ti,ab,kw
#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#3 and #12 with Cochrane Library publication date Between Jan 2010 and Oct 2019

Database: CRD HTA (Centre for Reviews and Dissemination, National Institute for Health Re search)
MeSH DESCRIPTOR Prostatic Neoplasms EXPLODE ALL TREES
((prostat* near4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or lump* or masses* or sarcom* or metastas*)))
#1 OR #2
MeSH DESCRIPTOR Hydrogels EXPLODE ALL TREES
MeSH DESCRIPTOR Polyethylene Glycols EXPLODE ALL TREES
MeSH DESCRIPTOR Hyaluronic Acid EXPLODE ALL TREES
MeSH DESCRIPTOR Collagen EXPLODE ALL TREES
((hydrogel* or hydrodissect* or DuraSeal or (polyethylene near3 glycol*) or liquid-to-solid))
((spacer* or spacing or spaceOAR or (separat* near8 prostat* near3 rectum) or ProSpace or ((biodegradable or bioresorbable) near3 polymer) or (biodegradable near3 balloon*) or (hyaluconic adj3 acid*) or collagen))
(((perirect* or rect* or prostate-rect* or denonvillier* or transperineal*) near4 space*))
#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#3 AND #11

Database: Epistemonikos
Date: 2019.10.02
Search results: 15
Search:
((SpaceOAR* OR DuraSeal* OR spacer* OR spacing OR "prostate-rectum" OR "prostate/rectum" OR hydrogel OR liquid-to-solid OR hydrodissect OR Polyethylene Glycol* OR “biodegradable polymer” OR “bioresorbable polymer” OR “biodegradable balloon*” or “hyaluconic acid*” OR collagen) AND (prostate OR prostatic))

GIN (Guidelines International Network)
Date: 2019.10.02
Search results: 0
Search: rectum spacer; rectal spacer; spaceoar; duraseal

PROSPERO
Date: 2019.10.02
Search results: 0
Search: rectum spacer; rectal spacer; spaceoar; duraseal

POP (Planned and Ongoing Projects)
Date: 2019.10.02
Search results: 0
Search: rectum spacer; rectal spacer; spaceoar; duraseal

Database: ClinicalTrials.gov/
Date: 2019.10.02
Search results: 16
Search: rectum spacer; rectal spacer; space*; spaceoar; duraseal

Database: ICTRP (WHO International Clinical Trials Registry Platform)
Date: 2019.10.02
Search: rectum spacer; rectal spacer; space*; duraseal
Hits: 9

Search II: Primary studies Search date: 2019.11.11.-12. Name of database	Hits	
	Results in each database Including duplicates	Without duplicates
Cochrane Library: Trials (CENTRAL)	67	
MEDLINE	183	
AMED (Ovid)	0	
Embase	1210	
Epistemonikos	195	
Total	1655	1384
Devices@FDA	0	-
Ongoing projects and trials		
Clinical Trials (US)	29	
ICTRP (WHO)	31	
Total	60	38
American Society of Clinical Oncology conference abstracts	16	2
Radiation Therapy Oncology Group (RTOG) clinical trials protocols	1	-
Total	1791	1424

Search strategies: Search II

Note: The search strategy is based on the search strategy for systematic reviews (2019-10-07) *without* collagen and duraseal, which were considered not relevant
We used no search filter for study design
Year limit: 2010-2019

Databases: **Embase** 1974 to 2019 November 11;
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)

exp Prostatic Neoplasms/
(prostat* adj4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or lump* or masses* or sarcom* or metastas*)).ti,ab,kw,kf.
prostate tumor/ [Embase]
or/1-3
Hydrogels/ use ppezv or hydrogel/ use oemezd
Hydrogel, Polyethylene Glycol Dimethacrylate/ use ppezv or polyethylene glycol dimethacrylate hydrogel/ use oemezd
Hyaluronic Acid/
Polyethylene Glycols/ use ppezv or macrogol derivative/ use oemezd
(hydrogel* or hydrodissect* or (polyethylene adj3 glycol) or liquid-to-solid).ti,ab,kw,kf.
(spacer* or spacing or spaceOAR or (separat* adj6 prostat* adj3 rect*) or ProSpace or ((biodegradable or bioresorbable) adj3 polymer) or ((biodegradable or rect*) adj3 balloon*) or (hyaluronic adj3 acid)).ti,ab,kw,kf.
((perirect* or rect* or prostate-rect* or denonvillier* or transperineal*) adj4 space*).ti,ab,kw,kf.
or/5-11
4 and 12
limit 13 to yr="2010 -Current"
Animals/
Humans/
15 not (15 and 16)
(news or editorial or comment).pt.
(letter or editorial or note).pt.
14 not (or/17-19)
remove duplicates from 20
21 use ppezv
21 use oemezd

Database: Cochrane Library
MeSH descriptor: [Prostatic Neoplasms] explode all trees
prostat* near/4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or lump* or masses* or sarcom* or metastas*)):ti,ab,kw
#1 or #2
MeSH descriptor: [Hydrogels] this term only
MeSH descriptor: [Hydrogel, Polyethylene Glycol Dimethacrylate] this term only
MeSH descriptor: [Hyaluronic Acid] this term only
MeSH descriptor: [Polyethylene Glycols] this term only
(hydrogel* or hydrodissect* or (polyethylene near/3 glycol*) or liquid-to-solid):ti,ab,kw
(spacer* or spacing or spaceOAR or (separat* near/6 prostat* near/3 rect*) or ProSpace or ((biodegradable or bioresorbable) near/3 polymer) or ((biodegradable or rect*) near/3 balloon*) or (hyaluconic near/3 acid*)):ti,ab,kw
((perirect* or rect* or prostate-rect* or denonvillier* or transperineal*) near/4 space*):ti,ab,kw
#4 or #5 or #6 or #7 or #8 or #9 or #10
#3 and #11 with Cochrane Library publication date Between Jan 2010 and Oct 2019

Database: Epistemonikos
(title:(SpaceOAR* OR spacer* OR spacing OR "prostate-rectum" OR "prostate rectum" OR hydrogel OR liquid-to-solid OR hydrodissect OR Polyethylene Glycol* OR "biodegradable polymer" OR "bioresorbable polymer" OR "biodegradable balloon*" OR "hyaluconic acid*" OR perirect* OR rect* OR prostate-rect* OR denonvillier* OR transperineal*) OR abstract:(SpaceOAR* OR spacer* OR spacing OR "prostate-rectum" OR "prostate rectum" OR hydrogel OR liquid-to-solid OR hydrodissect OR Polyethylene Glycol* OR "biodegradable polymer" OR "bioresorbable polymer" OR "biodegradable balloon*" OR "hyaluconic acid*" OR perirect* OR rect* OR prostate-rect* OR denonvillier* OR transperineal*)) AND (title:("prostate cancer*" OR "prostatic cancer*" OR "prostate neoplasm" OR "prostatic neoplasm*" OR

adenocarcinoma) OR abstract:("prostate cancer*" OR "prostatic cancer*" OR "prostate neoplasm" OR "prostatic neoplasm*" OR adenocarcinoma))

Database: WHO ISTRP **(WHO International Clinical Trials Registry Platform)**
Hits: 29
Search:
#1: prostatic AND spacer; prostate AND spacer;
#2: prostate neoplasms AND hydrogel
#3: prostate AND cancer AND balloon
#4: rectum AND spacer
#5: duraseal; spaceoar

Database: ClinicalTrial.gov
Search date: 2019-11-18
Hits: 31
Search:
#1: prostatic AND spacer; prostate AND spacer;
#2: prostate neoplasms AND hydrogel
#3: prostate AND cancer AND balloon
#4: rectum AND spacer
#5: duraseal; spaceoar

American Society of Clinical Oncology conference abstracts
(https://meetinglibrary.asco.org/);
Search date: 2019-11-18
Hits: 16 hits, 2 unique
Searches (Keywords):
#1: prostate AND spacer
#2: rectum AND spacer)
#3: prostate AND balloon
#4: biodegradable balloon
#5: prostate AND gel

Radiation Therapy Oncology Group (RTOG) clinical trials protocols
(www.rtog.org/ClinicalTrials/Welcome.aspx)
Search date: 2019-11-18
Search: Disease Sites Table Minimize; RTOG Genitourinary Cancer Studies; Prostate
Hits: 1

Database: Devices@FDA
Search date: 2019-11-18
Hits: 0

DESCRIPTION OF THE EVIDENCE USED

Evidence tables of individual studies included for clinical effectiveness and safety

Table A1: Characteristics of randomized controlled studies

First author	**Mariados N, [Pieczonka C 2015, Hamstra, DA 2017 Hamstra 2018, Fisher-Valuck 2017]**
Year of publication	2015
Clinical trial identification number	NCT01538628
Sponsorship source and role of funder	The study was supported by research funding from Augmenix.
City, country of patient recruitment	United States (multicentre)
Setting	Not reported
Article language	English
Declaration of interest	Two authors are shareholders and 1 author received speaking honoraria from the manufacturer. 2 authors have provided consulting services. Drs Mariados and Shah have each made small investments in Augmenix. Dr Sylvester has received a speaking honorarium and equity from Augmenix. Dr Hamstra and Ms Daignault-Newton have provided consulting services for Augmenix.
Contact with authors	No
Study design	RCT
Type of analysis	2015 Mariados paper: Differences in spacer and control patients experiencing declines in quality of life were determined using the Chi-square x^2 test. The power for the primary effectiveness endpoint that at least 70% of the spacer patients would achieve a ≥25% reduction in rV70 was 99.4%. The power for the primary safety endpoint, assuming endpoint event rates of 60% and 40% for the control and spacer groups, respectively, was 80.8%. The overall probability that both null hypotheses would be rejected was at least 80.2%. Authors used two-sample t-test for continuous variables and the Fisher exact test for categorical data. 2015 Pieczonka paper: Differences between spacer and control demographics and cancer statistics were determined using the 2-sample t-test for continuous variables and Fisher's test for categorical data. Exact binomial test was used to determine statistical significance, the Cochran-Mantel Haenzel and chi-square test were used for toxicity severity and quality of life group comparisons. 2017 Hamstra paper (3 years) cumulative incidence of late toxicity was evaluated using the log-rank test and Kaplan Meier analysis. For QoL, the mean changes in the EPIC summary scores from baseline were evaluated in linear mixed models. Pairwise testing was done within the modelling framework. MID were evaluated according to published thresholds 2018 Hamstra paper (secondary analysis of a phase 3), mean changes for the EPIC summary scores were evaluated in a linear mixed model with fixed effects – pairwise testing was done within the modelling framework Fischer-Valuck 2017: Student t-test was used to evaluate the statistical significance between the Symmetry 1 and other Symmetry groups

	regarding rectal dose reduction and the difference between pre- and post-spacer rectal dose for each Sym group. The Fisher exact test was used to determine the statistical significance between hydrogel Rectal Wall Infiltration and procedural adverse events and with acute and late rectal toxicity. A p value of .05 was considered statistically significant.
Inclusion criteria	Men with stage T1 and T2 prostate cancer, a Gleason Score of <7, PSA concentration of 20 ng/ml, and a Zubrod performance status of 0–1, planning to have image guided intensity modulated radiotherapy (IG-IMRT) were included.
Exclusion criteria	Patients with a prostate volume of >80 cm3, extracapsular extension of disease or >50% positivity biopsy scores, metastatic disease, indicated for or had recent androgen deprivation therapy and prior prostate surgery or radiotherapy were excluded.
Number patients at baseline	222
Age at baseline	Spacer group 66.4 years; control group: 67.7 years
Tumour site	Prostate
Disease status	Not stated
Palpable tumour (%)	Spacer group 23%; control group 24.7%
Tumour grading at baseline	Intervention: Gleason Score of 6 = 64.4%; Gleason Score of 7 = 35.6% Control: Gleason Score of 6=50.7%; Gleason Score of 7 = 49.3%
TNM-stage	T1 (Tq, T1a, T1b, T1c) Intervention 63.8%; Control 68.5% T2 (T2, T2a, T2b, T2c) Intervention 36.2%; Control 31.5%
General description of intervention procedure	Using an aseptic transperineal technique, authors placed 3 gold intraprostate fiducial markers, and patients were immediately randomized (envelope opened) to receive transperineal injection of spacer or no injection as a control. Five to 10 days later, patients underwent a second CT and MRI for postprocedural IG-IMRT treatment planning Mariados 2015: No details of the insertion procedure Pieczonka 2015: All placement procedures (fiducial placement with or without hydrogel injection) were performed in the outpatient setting following bowel preparation. Patients in the lithotomy position were anaesthetized according to standard of care and the perineal skin was prepped for an aseptic procedure. Using a stepper mounted side-fire transrectal ultrasound probe 3 to 4 fiducial markers were placed into the prostate via the transperineal approach. Patients in the spacer group had the transrectal ultrasound probe lowered, reducing compression of the perirectal space in anticipation of spacer application. Using the transperineal approach an 18G x 15 cm needle was inserted approximately 1 to 2 cm above the anal opening, and advanced at a slight angle to the perirectal fat between the anterior rectal wall and the prostate. After confirmation of midline needle tip positioning in the midline perirectal fat, saline was injected (hydrodissection) to verify that the needle was not in the rectal wall or anterior to Denonvilliers' fascia. Aspiration was then performed to verify the tip was not intravascular, and the saline syringe was removed and replaced with the SpaceOAR applicator. Using a smooth, continuous technique, the hydrogel precursors were injected into the perirectal space, and the needle was removed and discarded. Antibiotic prophylaxis was administered to 95.2% and 94.5% of patients in the spacer and control groups. Forms of anaesthesia included general (36% and 35.6%), local (32% and 30.1%), monitored anaesthesia care (25.4% and

	26%) and conscious sedation (4.8% and 6.8%) in the spacer and control groups.
Description of comparator	Same as above without the transperineal injection of hydrogel spacer
Detailed description of intervention (hydrogel)	"The most widely studied of these materials is a novel polyethylene glycol hydrogel that expands the perirectal space as an injected liquid and then polymerizes (solidifies) into a soft, absorbable spacer (SpaceOAR™ system). The hydrogel spacer has been shown to be stable throughout the typical course of radiation therapy, resulting in a significant decrease in rectal irradiation and encouraging acute and late outcomes."
Detailed description of radiotherapy	"The prescription dose was 79.2 Gy at 1.8 GY per fraction, delivered to ≥98% of the planning target volume (PTV) and 100% of the clinical target volume, with the clinical target volume maximum of ≤110% of the prescription dose. PTV margins were institutionally determined within protocol-defined limits of 5 to 10 mm, and normal rectal dose constraint objectives for 15%, 20%, 25%, 35%, and 50% of the rectal volume were <75 Gy, <70 Gy, 65 Gy, 60 Gy and <50 Gy respectively per quantitative of analysis of normal tissue effects in the clinic guidelines."
Description of any other concomitant treatments	None mentioned
Follow up times	Mariados 2015: baseline, 3,6,12 and 15 months Hamstra 2017: 3 years

Table A2: Characteristics of nRCT study

First author	**Wolf**
Year of publication	2015
Clinical trial identification number	None found
Sponsorship source and role of funder	Spacer materials were kindly provided by Augmenix and BioProtect, respectively
City, Country of patient recruitment	Austria
Setting	Not reported
Article language	English
Declaration of interest	Yes – No conflicts of interest are declared.
Contact with authors	No
Study design	Non-randomized controlled trial
Type of analysis	Completers Statistical difference of volume reduction between groups were tested using a single-sided paired Student's t-test choosing a significance level of p=.01. Statistical differences of toxicities were carried out using Chi-squared test (Brandt-Snedecor) for CTC scoring and Kruskal-Wallis test for VRS scoring at a significance level of p=.05.

Inclusion criteria	78 patients eligible for primary radiation of the prostate in the period from 05/2012 until 07/2013 were included in the study.
Exclusion criteria	Intrinsic contraindications such as compulsory anticoagulation therapy or severe co-morbidities preventing them having anaesthesia -- Patients with hip transplants were excluded from the study.
Number patients at baseline	n=78 (30 spacer gel group versus 29 balloon spacer group versus 19 control group) For balloon spacer volume dynamics assessment, a separate group of 18 patients who had the spacer were analysed
Age at baseline	Not reported
Tumour site at baseline	Prostate
Disease status at baseline	None mentioned
Palpable tumour	Not mentioned
Tumour grading	None stated
TNM-stage	None stated
General description of intervention	The application of both spacers was performed by urologists in a short general anaesthesia according to the manufacturer's protocol. The type of spacer was selected in a random fashion at the physician's discretion. Balloons were filled with either NaCl 0.9% or a mixture of NaCl and contrast agent (Visipaque 270 mg J/ml, GE Healthcare) at a ratio of 1:4. In the same session, four gold marker fiducials were inserted into the prostate under rectal ultrasound guidance.
General description of comparator	19 patients not eligible for spacer application due to intrinsic contraindications such as compulsory anticoagulation therapy or severe co-morbidities preventing them having anaesthesia served as a control group.
Detailed description of spacer	SpaceOAR™ System (Augmenix Inc., Waltham, MA) is a PEG gel that polymerizes in seconds creating a hydrogel space. Following hydrodissection with a saline solution and confirmation of proper needle location, the two liquid hydrogel precursors are injected where they expand the perirectal space and then polymerize. The water and PEG composition result in a high degree of tissue compatibility without local or systemic toxicity. It maintains space for approximately three months and is compression-resistant. The hydrogel should be absorbed in approximately six months, with the degradation products cleared via renal filtration.

	ProSpace™ (BioProtect Inc., Kfar-Saba, Israel) Balloon is composed of biodegradable polymers. Once the balloon is in situ, it is inflated with sterile saline to reach its final configuration. The balloon remains inflated during the entire treatment period and allegedly biodegrades in the body within 3–6 months.
Detailed description of radiotherapy	Total dose was 75.85 Gy in daily fractional doses of 1.85 Gy prescribed to the 95% isodose using multisegmental 7-field and shoot IMRT.
Description of any other concomitant treatments	None mentioned
Follow-up period	6 months

Table A3: Characteristics of other relevant studies – Trial registry records

List of ongoing and planned studies

Study Identifier	Status	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02353832 [28] University of Texas	Active, not recruiting	Single Group	44	Hydrogel	none	Low Risk Prostate Cancer	Percentage of participants with reduction in acute periprostatic rectal ulcer events from 90%+ to <70% Effectiveness of space creation of >= 7.5 mm in protecting rectum from toxicity Spacer related acute toxicity Spacer stability by dimensions
NCT03663218 [29] In Abstract	Active, not recruiting	Sequential Assignment *single arm	40	Radiation, dose escalation Unclear: “placement of a rectal spacer“	none	Male patients with a diagnosis of high-risk prostate cancer	Assessing if patients can undergo a radical prostatectomy after SBRT without a post-operative gastrointestinal or urinary grade 3 or above toxicity Acute toxicity in patients after stereotactic body radiotherapy (SBRT) and radical prostatectomy Quality of life scores 5 years
NCT00918229 [30]	Completed	Single Arm	24	BioProtect Biodegradable Implantable Balloon	none	male above 45 years old and less than 85, locally confined prostate cancer	Proportion of subjects achieving a reduction of at least 25% of the volume of the rectum receiving at least 70 Gy Rate of occurrence of grade 2 or greater rectal adverse event or procedure-related adverse events.
NCT01538628 [8] Companion to Mariados 2015	Completed	RCT	222	Hydrogel	Non-hydrogel	Subjects must have clinical stage T1 or T2 as determined from a biopsy Gleason Score	Proportion of subjects achieving a reduction of 25% or greater in percent volume of the rectum receiving at least 70 Gy

Study Identifier	Status	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
						less than or equal to 7, age 18 and older	Proportion of subjects experiencing a Grade 1 or greater rectal adverse event or procedure adverse event Proportion of subjects experiencing a Grade 2 or greater rectal adverse event or procedure adverse event
NCT02212548 [31] Linked to Juneja 2015 and vanGysen 2013	Completed	Single Arm	30	Hydrogel	None	Child, adult and older adult,	% volume of rectum receiving 40 Gy, 65 Gy, 70 Gy, 75 Gy and 80 Gy Evaluation of serious adverse events or complications secondary to PEG hydrogel insertion. Gastrointestinal toxicity
JPRN UMIN000038131 [33]	No longer recruiting	Single Arm	46	Hydrogel	None	Men undergoing LDR Brachytherapy monotherapy for localized Prostate Cancer in accordance with the IFU and Appropriate Use Document	Mean mid gland (axial) perirectal space following SpaceOAR™ hydrogel implantation (mm). Change in prostate dimensions before and after SpaceOAR™ placement.
UMIN000026213 [32]	No longer recruiting	Single Arm	42	Hydrogel	Historical	Male 20 to 80 years, diagnosed with adenocarcinoma, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) grade 0-2	Safety, Efficacy All acute gastrointestinal toxicity
ACTRN12612000524897 [34]	Not yet recruiting	Single Arm	40	Hydrogel	Historical	Histopathologically confirmed, localised prostate cancer, 50 to 75yrs	Feasibility of PEG Hydrogel in increasing prostate-rectum separation and improving rectal dosimetry in prostate brachytherapy and/or external beam radiotherapy patients

Study Identifier	Status	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							Safety of transperineal PEG Hydrogel injection Rectal toxicity Stability of PEG Hydrogel and durability of prostate-rectum separation Quality of life following prostate brachytherapy and/or external beam radiotherapy
NCT03525262 [36] University of Texas	Recruiting	RCT	120	Hydrogel	SAbR WITHOUT neurovascular sparing	Adults 18 to 120 years, clinical stage T1 (a, b, or c) or T2 (a, b, or c) adenocarcinoma of the prostate	Reduction in Expanded prostate cancer index composite (EPIC) sexual function Acute & Delayed Genitourinary (GU) and Gastrointestinal (GI) toxicity Biochemical failure RTOG-ASTRO definition
NCT03400150 [35]	Recruiting	RCT	222	Balloon	Standard of care for prostate cancer	Invasive adenocarcinoma of the prostate, at clinical stage T1-T3	Adverse event rate of occurrence Reduction in rectal radiation exposure
NCT03386045 [37]	Recruiting	RCT	214	Hydrogel	Either moderate hypo-fractionation or SBRT	Adenocarcinoma, ECOG performance status 0 to 2	The rate of local control as determined on PSMA scanning Biological failure rate Late toxicity Markerless tracking technology Accuracy of the various intrafraction guidance methods
NCT02478112 [38]	Suspended (lack of recruitment)	Single Arm	24	Balloon	none	localized adenocarcinoma of the prostate	Dosimetric gain from the contribution of the balloon on organs at risk Urinary and rectal toxicity

Study Identifier	Status	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							Stages of the implantation of the BioProtect balloon Technical feasibility of the implantation of the BioProtect balloon Quality of life by QLQ-C30
NCT01999660 or DRKS00006409 [39]	Unknown	Case Control	250	Hydrogel	unclear	Patient is suffering from pathologically confirmed T1-T2, N0, M0 prostate adenocarcinoma.	The rectal complication rate (late toxicity) Quality of life Feasibility of the implantation procedure
NCT02165020 [40]	Unknown	Non-randomized	36	Hyaluronic Acid	None	Patient with a low- to intermediate-risk prostate cancer, according to D'Amico classification	Number of patients with late rectal toxicities (> 3 months) of grade ≥ 2 after hypofractionated radiotherapy of prostate cancer of 62 Gy in 20 fractions of 3.1 Gy Number of patients with acute rectal toxicities of all grades and of grade ≥ 2. Tolerance of the HA injection Number of patients with acute and late toxicities, other than the rectal toxicities. The evaluation of the biochemical control
NCT02361515 [41]	Unknown	RCT	96	Hyaluronic Acid	Moderate hypofractionated radiotherapy of 62 Gy	Patient with a low- to intermediate-risk prostate cancer, according to D'Amico classification	Number of patients with late urinary toxicities of grade ≥ 2 after moderate hypofractionated radiotherapy (62 Gy in 20 fractions of 3.1 Gy) and after SBRT (37.5 Gy in 5 fractions of 7.5 Gy). Survival rates without biological relapse in both arms

Study Identifier	Status	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							Acute urinary and rectal toxicities in both arms Sexual preservation rates in both arms Late rectal toxicities in both arms

LIST OF INCLUDED (AND NOT PROCESSED) STUDIES

Table A4: List of single-arm, abstract and poster studies

Study Identifier	Intervention	Number of Comparisons	Publication Type
Alfieri 2014 [131]	Hydrogel or SpaceOAR™	Single Arm	Poster
Alongi 2013 [132]	Hydrogel or SpaceOAR™	Single Arm	Full Text
Baghwala 2019 [133]	Hydrogel or SpaceOAR™	Comparator	Abstract
Barnes 2013 [134]	Unclear	Single Arm	Poster
BenYosef 2013 [135]	Balloon	Single Arm	Poster
Boissier 2017 [136]	Hyaluronic Acid	Single Arm	Full Text
Castellano 2012 [137]	Hydrogel or SpaceOAR™	Single Arm	Abstract
Cavanaugh 2016 [138]	Hydrogel or SpaceOAR™	Comparator	Poster
Cavanaugh 2018 [139]	Hydrogel or SpaceOAR™	Comparator	Abstract
Chao 2018 [140]	Hydrogel or SpaceOAR™	Single Arm	Poster
Chao 2018 [141]	Hydrogel or SpaceOAR™	Single Arm	Poster
Chao 2019 [142]	Hydrogel or SpaceOAR™	Single Arm	Full Text
Chapet 2013 [143]	Hyaluronic Acid	Single Arm	Poster
Chapet 2015 [144]	Hyaluronic Acid	Single Arm	Full Text
Chapet 2016 [145]	Hyaluronic Acid	Single Arm	Poster

Study Identifier	Intervention	Number of Comparisons	Publication Type
Costa 2018 [115]	Balloon	Single Arm	Poster
Dal Moro 2011 [146]	Balloon	Single Arm	Poster
Dovda 2019 [147]	Hydrogel or SpaceOAR™	Single Arm	Poster
Eade 2016 [116]	Hydrogel or SpaceOAR™	Single Arm	Poster
Eckert 2013 [148]	Hydrogel or SpaceOAR™	Single Arm	Full Text
Fairmichael 2018 [149]	Hydrogel or SpaceOAR™	Single Arm	Poster
Folkert 2017 [150]	Hydrogel or SpaceOAR™	Single Arm	Abstract
Garg 2011 [151]	Balloon	Single Arm	Poster
Gez 2013 [126]	Balloon	Single Arm	Full Text
Greco 2012 [152]	Hydrogel or SpaceOAR™	Single Arm	Poster
Hartsell 2019 [153]	Hydrogel or SpaceOAR™	Single Arm	Poster
Hatiboglu 2011 [154]	Hydrogel or SpaceOAR™	Single Arm	Poster
Hatiboglu 2014 [155]	Hydrogel or SpaceOAR™	Single Arm	Poster
Ho 2016 [112]	Hydrogel or SpaceOAR™	Single Arm	Abstract
Hojjat 2016 [156]	Balloon	Single Arm	Abstract
Hojjat 2019 [157]	Balloon, Hydrogel or SpaceOAR™	Single Arm	Abstract
Hruby 2014 [158]	Balloon	Single Arm	Abstract
Jones 2017[159]	Unclear	Unclear - uses data from two trials	Abstract
Kalogeropoulos 2012 [160]	Balloon	Single Arm	Abstract
Khalil 2017 [161]	Hydrogel or SpaceOAR™	Single Arm	Abstract
King 2018 [162]	Hydrogel or SpaceOAR™	Single Arm	Full Text
Kishi 2012 [163]	Hyaluronic Acid	Comparator	Abstract
Kleiven 2017 [164]	Hydrogel or SpaceOAR™	Single Arm	Abstract
Klotz 2013 [165]	Hydrogel or SpaceOAR™	Single Arm	Full Text - German

Study Identifier	Intervention	Number of Comparisons	Publication Type
Kouloulias 2013 [166]	Balloon	Single Arm -prospective-retrospective	Full Text
Kovacs 2010 [167]	Balloon	Single Arm	Abstract
Latorzeff 2018 [168]	Hydrogel or SpaceOAR™, Balloon, Hyaluronic Acid	Single Arm	Abstract
Loganathan 2019 [169]	Hydrogel or SpaceOAR™	Comparator	Abstract
Malouf 2013 [170]	Hydrogel or SpaceOAR™	Single Arm	Abstract
Mathers 2013 [171]	Hydrogel or SpaceOAR™	Single Arm	Abstract
McCarthy 2019 [172]	Hydrogel or SpaceOAR™	Single Arm	Abstract
Melchert 2011 [173]	Balloon	Single Arm	Poster
Ogita 2019 [174]	Hydrogel or SpaceOAR™	Single Arm	Abstract
Pinkawa 2011 [175]	Hydrogel or SpaceOAR™	Single Arm	Full Text
Pinkawa 2013 [176]	Hydrogel or SpaceOAR™	Single Arm	Abstract
Pinkawa 2014 [177]	Hydrogel or SpaceOAR™	Single Arm	Abstract
Pinkawa 2016 [178]	Hydrogel or SpaceOAR™	Single Arm	Full Text
Pinkawa 2018 [179]	Hydrogel or SpaceOAR™	Comparator	Abstract
Prada 2012 [180]	Hyaluronic Acid	Single Arm	Full Text
Prada 2018 [181]	Hyaluronic Acid	Single Arm	Full Text
Saigal 2019 [182]	Hydrogel or SpaceOAR™	Comparator	Abstract
Sanchez Iglesias 2013 [183]	Balloon	Single Arm	Abstract
Shapiro 2018 [184]	Hydrogel or SpaceOAR™	Single Arm	Poster
Tagliagamba 2013 [185]	Hydrogel or SpaceOAR™	Single Arm	Abstract
Thomas 2019 [114]	Balloon	Single Arm	Poster
Uhl 2011 [186]	Hydrogel or SpaceOAR™	Single Arm	Abstract
Uhl 2012 [187]	Hydrogel or SpaceOAR™	Single Arm	Abstract
Uhl 2013 [188]	Hydrogel or SpaceOAR™	Single Arm	Full Text

Study Identifier	Intervention	Number of Comparisons	Publication Type
Uhl 2014 [124]	Hydrogel or SpaceOAR™	Single Arm	Full Text
Usnami 2019 [189]	Hydrogel or SpaceOAR™	Single Arm	Abstract
Van Gysen 2013 [190]	Hydrogel or SpaceOAR™	Single Arm	Full Text
Van Gysen 2014 [191]	Hydrogel or SpaceOAR™	Single Arm	Full Text
Vanneste 2018 [192]	Balloon	Single Arm	Full Text
Vanneste 2019 [193]	Hydrogel or SpaceOAR™	Single Arm	Full Text
Vassilis 2013 [194]	Balloon	Single Arm	Full Text
Whalley 2016 [195]	Hydrogel or SpaceOAR™	Single Arm	Full Text
Wilder 2010 [196]	Hyaluronic Acid	Single Arm	Full Text
Wu 2018 [197]	Hydrogel or SpaceOAR™	Comparator	Abstract
Yeh 2016 [198]	Hydrogel or SpaceOAR™	Single Arm	Abstract

List of excluded studies

Table A5: List of excluded studies with reasons

Study Identifier	Reason for exclusion
Abstract (no NCT#) [199]	Wrong intervention
ACTRN12615000223 2015 [200]	Wrong comparator
ACTRN12617000035 2017 [201]	Wrong patient population
ACTRN12618000934 2018 [202]	Wrong intervention

Study Identifier	Reason for exclusion
Aditama 2015 [203]	Wrong study design
Aherne 2019 [204]	No data
Alongi 2014 [205]	No data
Alongi 2014 [206]	No data
Alonzi 2018 [207]	Wrong outcomes
Aminsharifi 2019 [208]	Wrong study design
Anders 2016 [209]	Wrong outcome
Aranguena Penacoba 2017 [210]	Wrong study design
Aranguena Penacoba 2018 [211]	Wrong study design
Hassan Rezaeian 2017 [212]	Wrong comparator
Australian Safety and Efficacy Register of New Interventional Procedures [213]	Wrong study design
Biagioli 2013 [214]	Wrong study design
Boike 2011 [215]	Wrong outcomes
Bosch 2015 [216]	Wrong intervention
Cavanaugh 2017 [217]	Wrong study design
Cavanaugh 2018 [218]	Wrong study design
Chao 2019 [219]	Wrong study design
Chao 2019 [220]	No text
Chao 2019 [221]	Wrong study design
Chapet 2012 [222]	Wrong outcome
Chapet 2013 [143]	Wrong outcome
Chapet 2014 [223]	Wrong outcome

Study Identifier	Reason for exclusion
Chapet 2017 [224]	Wrong study design
Chittenden 2011 [225]	Wrong study design
Chung 2017 [226]	Wrong intervention
Crehange 2018 [227]	Wrong patient population
Crehange 2018 [228]	Wrong patient population
Eade 2017 [229]	No data
Fagundes 2015 [230]	Wrong outcomes
Fairmichael 2019 [231]	Wrong study design
Fersino 2016 [232]	Wrong patient poulation
Gannavarapu 2019 [233]	Wrong outcomes
Garcia Perez 2019 [234]	Wrong patient population
Guimas 2016 [235]	Wrong study design
Habl 2016 [236]	Wrong study design
Hayes 2015 [237]	Wrong study design
Heemsbergen 2017 [238]	Wrong intervention
Hong 2011 [239]	Wrong intervention
Huang 2016 [240]	Wrong outcome
Huang 2016 [241]	Wrong outcome
Hwang 2018 [242]	Wrong study design
Hwang 2019 [243]	Wrong study design
Jones 2017 [244]	Wrong study design
Jones 2017 [245]	Wrong comparator
Kametriser 2013 [246]	Wrong outcomes

Study Identifier	Reason for exclusion
Kim 2017 [247]	Wrong intervention
Kishi 2012 [248]	Wrong study design
Leiker 2018 [249]	Wrong study design
Lerner 2019 [250]	Wrong outcomes
Levra 2015 [251]	Wrong patient population
Liu 2017 [252]	Wrong intervention
Lyons 2016 [253]	Wrong intervention
Mah 2013 [254]	Wrong intervention
Mahal 2014 [255]	Wrong patient population
Mascarenhas 2015 [256]	Wrong outcomes
Mastroianni 2014 [257]	Wrong outcome
Melchert 2013 [173]	Wrong outcome
Mok 2014 [258]	Wrong study design
Morita 2019 [259]	Wrong study design
Ng 2012 [260]	Wrong intervention
Ng 2014 [261]	Wrong study design
Nihr 2014 [262]	Wrong study design
Noyes 2012 [263]	Wrong intervention
Ogita 2019 [264]	Wrong outcome
Pinkawa 2011 [265]	Wrong outcomes
Pinkawa 2012 [266]	Wrong study design
Pinkawa 2012 [267]	Wrong study design
Pinkawa 2013 [268]	Wrong outcome

Study Identifier	Reason for exclusion
Pinkawa 2014 [269]	Wrong study design
Pinkawa 2017 [45]	Wrong study design
Pryor 2019 [270]	No data
Pryor 2018 [271]	Wrong patient population
Pryor 2019 [272]	No data
Rucinski 2015 [273]	Wrong study design
Sanders 2018 [274]	No data
Sanguineti 2019 [275]	Wrong intervention
Schorghofer 2019 [276]	Wrong comparator
Schorghofer 2019 [277]	Wrong comparator
Sedlmayer 2012 [278]	Wrong study design
Serrano 2017 [279]	Wrong study design
Seymour 2019 [117]	Wrong study design
Seymour 2019 [280]	Wrong study design
Singh 2017 [281]	Wrong study design
Song 2011 [282]	Wrong outcomes
Spira 2012 [283]	Wrong intervention
Stefanelli 2012 [284]	Wrong study design
Stephans 2016 [285]	Wrong intervention
Strom 2014 [125]	Wrong intervention
Taggar 2018 [286]	Wrong study design
Tang 2018 [287]	Wrong study design
Tokita 2011 [288]	Wrong intervention

Study Identifier	Reason for exclusion
Udrescu 2012 [289]	Wrong outcomes
Valero Albarran 2013 [290]	Wrong study design
Valvo 2019 [291]	Wrong patient population
Vargas 2016 [292]	Wrong intervention
Weill Medical College [293]	Wrong intervention
Weill Medical College 2018 [294]	Wrong comparator
Woo 2013 [295]	Wrong study design
Yeh 2016 [296]	Wrong intervention
Zilli 2010 [297]	Wrong intervention
Zilli 2014 [298]	Wrong study design
Patmanabhan 2017 [299], Pinkawa 2014 [269], Roach 2018 [300], Schutzer 2015 [301], Triffileti 2016 [302], Valdagni 2013 [303], Aminsharifi 2019 [208], Anonymous 2018 [199], Hatiboglu 2013 [304], Heikkila 2014 [305], Hutchinson 2016 [306], Kainhar 2018 [307], Kim 2017 [308], Biagoli 2013 [214], Fersino 2016 [232], Nguyen 2014 [309],	Saved and used to check references and as background papers

Risk of bias tables

Table A6: Risk of bias – study level (RCTs)

Trial	Random sequence generation	Allocation concealment	Blinding				Incomplete outcome data	Selective outcome reporting	Other bias	Risk of bias – overall judgement
			Patient	Outcome assessment subjective	Outcome assessment objective	Who deliver the intervention				
Mariados 2015	L[1]	L[1]	L	L[2]	L[2]	H[2]	H[3]	H[4]	L	H[5]

Footnotes:
1 Assessment completed with additional information provided by Manufacturer, available from Boston Scientific upon request.
2 Personnel (assessors and who delivers the intervention) were not blinded for the allocated treatment (not possible to blind). While outcome assessors were not blinded, for the All IG-IMRT planning documentation and CT and MRI, scans were forwarded to a blinded, independent core laboratory for verification and patients were blinded.
3 High attrition at 3 yrs follow-up (Hamstra 2017).
4 Discrepancies between trial registry outcomes and some publications associated with the trial - Trial Registry number = NCT01538628.
5 High risk based on judgements for blinding, incomplete outcome data, and selective reporting.

Abbreviations: L= Low Risk, H= High Risk

Table A7: Risk of bias – study-level of nRCT

Trial	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Wolf 2015	Serious[1]	Moderate to Serious[2]	Low	Low	No information	Moderate[3]	No information[4]	Serious

Footnotes:

1 Risk of bias due to confounding is inherent in nRCT design; authors do not address confoundings.
2 Selection into the groups based on participants' characteristics (i.e. compulsory anticoagulation therapy, or severe co-morbidities).
3 Outcome assessors are aware of the intervention, different methods to assess outcomes in different groups (i.e. volume dynamics balloon).
4 No study protocols available for verification.

Table A8: Summary of findings tables

Effectiveness

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)		
Rectal Toxicity[1]												
1	RCT	Serious[1]	Not serious	Not serious	Serious[2]		148	71	3mo-G1 RR 0.77 (0.50 to 1.19) 3mo-G≥2 RR0.91 (0.23 to 3.5)	94 fewer per 1000 (from 204 fewer to 78 more) 6 fewer per 1000 (from 47 fewer to 152 more)	Low	Critical

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)		
									15 mo – G1 RR 0.34 (0.08 to 1.48) 15 mo - G≥2 RR 0.15 (0.01 to 3.71)	40 fewer per 1000 (from 56 fewer to 29 more) 13 fewer per 1000 (from 15 fewer to 41 more)		
	RCT	Very Serious[3]	Not serious	Not serious	Serious[2]	Lost to follow up 37%	94	46	36 mo -G1-HR 0.24 (0.06 to 0.97) 36-mo -G≥2 HR not available	Unable to calculate	Very low	Critical
1	nRCT	Serious[1]	Not serious	Not serious	Serious[2]	None	59	19	Gel -3 mo -G1 RR 1.58 (0.34 to 7.60)	61 more per 1000 (from 69 fewer to 695 more	Very low	Critical
									Balloon -3 mo -G1 RR 1.64 (0.35 to 7.60)	67 more per 1000 (from 68 fewer to 695 more)		
Urinary Toxicity[1]												
1	RCT	Serious[1]	Not serious	Not serious	Serious[2]		148	71	3mo- G1 RR 1.03 (0.87 to 1.21) 3 mo- G≥2 RR 0.97 (0.81 to 1.18)	25 more per 1000 (from 107 fewer to 173 more) 25 fewer per 1000 (from 156 fewer to 148 more)	Low	Critical
									15 mo – G1 RR 0.65 (0.15 to 2.85) 15 mo - G≥2	15 fewer per 1000 (from 36 fewer to 75 more)		

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)		
									RR 1.57 (0.44 to 5.53)	25 more per 1000 (from 23 fewer to 196 more)		
	RCT	Very Serious[3]	Not serious	Not serious	Serious[2]	Lost to follow up 37%	94	46	36 mo -G1- HR 0.36 (0.12 to 1.1) 36-mo -G≥2 HR 1.22 (0.40 to 3.72)	Unable to calculate	Very low	Critical
1	nRCT	Serious[1]	Not serious	Not serious	Serious[2]	None	59	19	Gel -3 mo -G2- RR 1.39 (0.57 to 3.38)	103 more per 1000 (from 113 to 626 more)	Very low	Critical
									Balloon – 3 mo – G2 RR 0.78 (0.27 to 2.12)	58 fewer per 1000 (from 192 to 295 more)		
Bowel QoL												
1	RCT	Serious[1]	Not evaluated	Not serious	Serious[2]	None	148	71	Summary Score: evidence suggest SpaceOAR™ +RT may improve bowel QoL (p = .002) over the entire follow up period.		Low	Critical
	RCT	Very serious	Not evaluated	Not serious	Serious[2]	Lost to follow up 37%	94	46			Very low	
Urinary QoL												
1	RCT	Serious[1]	Not evaluated	Not serious	Serious[2]	None	148	71	Evidence suggests no difference between groups over the entire follow-up time in urinary QoL (p=.13).		Low	Critical
	RCT	Very serious	Not evaluated	Not serious	Serious[2]	Lost to follow up 37%	94	46				
Sexual												
1	RCT	Very serious	Not evaluated	Not serious	Serious[2]	Lost to follow up 37%	94	46	sexual function was similar in both groups over the entire follow-up time between groups (p=.6)		Very low	Critical
Reduction in rectal radiation dose												
1	RCT	Serious[1]	Not serious	Not serious	Serious[2]	None	148	712	Not estimable		Low	Important

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)		
1	nRCT	Serious	Not serious	Not serious	Serious	None	59	19	Not estimable		Very low	
Increase distance between rectum-prostate												
1	RCT	Serious	Not evaluated	Not serious	Serious	None	148	72	Not estimable		Low	Important
PSA												
1	RCT	Serious	Not evaluated	Not serious	Serious	None	148	72	Not estimable	--	Low	Important
Overall survival - not measured in these studies												

Comments:

1 Assessed according to Common Terminology Criteria for Adverse Events (CTCAE v4).
2 Downgraded one level due to limitations in design (high risk of bias) (e.g. blinding, selective reporting)
3 Downgraded one level due to imprecision (one or two small studies)
4 Downgraded one level due to limitations in design (high risk of bias) (e.g. bias due to confounding, selection of participants, bias of measurement of outcome)
5 Downgraded two levels due to limitations in design (missing data without imputations with less than 300 patients included

Abbreviations: CI: Confidence Interval; HR hazard ratio; G1: grade 1 toxicity; G≥2: grade 2 or grater toxicity; RCT: randomized controlled trial; nRCT: non randomized controlled trial; RR risk ratio; RT: radiotherapy; QoL: Quality of life;

Safety

Quality assessment							Summary of findings					
							Number of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)		
Adverse event (grade 1 to 2)												
1	RCT	Serious[1]	Not serious	Not serious	Serious[2]	None	148	71	Narrative synthesis		Low	Important
1	nRCT								Not reported			
Adverse event (grade 3 to 4)												
1 and 1	RCT and nRCT								No grade 3 to 4 adverse events			Critical
Death related to adverse events												
1 and 1	RCT and nRCT								No death related to adverse events reported			Critical
1 Downgraded because of limitations described in the risk of bias table for RCTs (i.e. blinding, selective reporting, attrition). 2 Downgraded for imprecision (only one small study contributed data for this outcome) .												

Abbreviations: CI: Confidence Interval

Applicability tables

Table A9: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The target population for this assessment were adults (>18yrs) who had prostate cancer. We focused on both localized and metastatic prostate cancer but we included patients undergoing curative treatment only. The characteristics of the patients enrolled in the included studies were not well described, so we do not know to what extent they match our target population. The RCT was the only one describing age and tumour stage. Other comorbidities or patient characteristics were briefly described. The nRCT did not provide information about the population included. The appropriate selection of patients, or applicability and efficacy of the technology in a sub-group of patients with different conditions (e.g. inflammatory bowel disease), age groups, race, and tumour stage, is still unclear.
Intervention	The targeted intervention for this assessment was biodegradable rectal spacers for prostate cancer radiotherapy. This assessment included two of the three CE-approved technologies in Europe (hydrogel or SpaceOAR™ and balloon or BioProtect). We included studies conducted prospectively and which were comparative with current pathway of care (radiotherapy). There were no studies meeting our inclusion criteria and containing hyaluronic acid as an intervention.
Comparators	The studies used EBRT as the comparator treatment. This reflects the prevailing usual care within the period of the trial.
Outcomes	The RCT reported on the following effectiveness outcomes: rectal and urinary toxicity, QoL (sexual and bowel sub-scales), rectal dose, increase distance between rectum and prostate and PSA values. The nRCT reported on urinary and rectal toxicity and rectal dose. The follow-up time was 3,6,12,15 and 36 months for the RCT and up to 3 months for the nRCT. This includes most of the outcomes that the assessment team considered critical and important to decision-making. The assessment team also rated overall survival as important but this outcome was not evaluated in the studies. Only the RCT reported on procedural adverse events. The two studies used the CTCAE grading system. The nRCT also used the Vienna rectal toxicity scores (not reported in this study).
Setting	The RCT was a multicentre trial conducted in the United States. No other information was provided. There is no information about setting for the nRCT study.

APPENDIX 2: REGULATORY AND REIMBURSEMENT STATUS

Table A10: Regulatory status

Model	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (incl. expiry date for country of assessment)	Launched yes/no If no, include date of launch
SpaceOAR™ Hydrogel System for prostate cancer applications (Class III)	Europe	CE	Yes	The SpaceOAR™ System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space, it is the intent of the SpaceOAR™ System to reduce the radiation dose delivered to the anterior rectum. Hydrogel Polymers and Associated Accessories can be used as Spacers and/or Fillers for Oncologic Radiotherapy.	None	March 2010	Yes
	Australia	Therapeutic Goods Administration	Yes			January 2011	Yes
	USA	FDA	Yes			April 2015	Yes
	Canada	Health Canada	Yes			Februar y 2016	Yes
	Japan	Pharmaceutical and Medical Devices Agency	Yes			May 2017	Yes
ProSpace™ Balloon System	Europe	CE Mark	Yes	The ProSpace™ System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space, it is the intent of the ProSpace System to reduce the radiation dose delivered to the anterior rectum.	None	-	Yes
	USA	FDA	Undergoing clinical studies in the USA prior to FDA regulatory approval			-	Yes
Barrigel™	Europe	CE Mark	Yes	Barrigel™ is used to increase the distance between the prostate and the anterior rectal wall, with the intent to decrease radiation dose delivered to the rectum when treating prostate cancer with radiation	None	2014	Yes
	USA	FDA	Undergoing investigation prior FDA approval			-	Yes

Abbreviations: FDA = Food and drug Administration, CE Marking = is a certification mark that indicates conformity with health, safety, and environmental protection standards for products sold within the European Economic Area

Table A11: Summary of (reimbursement) recommendations in European countries for the technology

Country /Region	Status of reimbursement	Standard of care: yes/no	Please provide a link to the most recent data and local information sources (e.g. national guidelines/guidance/policy documents
Austria[1]	Not reimbursed	No	n.a.
Croatia[1]	Not reimbursed in public health sector	No	n.a.
France[1]	Reimbursed* as part of the DRG payment	Yes	Ongoing assessment. Final appraisal expected in March 2020
Germany[1]	Reimbursed**	Yes	
Hungary[1]	Not reimbursed in public health sector	No	n.a.
Italy[1]	Reimbursed***	Yes****	Ministry of Health, New Health Informative System (NSIS) (https://nsis-ids.sanita.it)
Italy/ Regione Emilia-Romagna[1]	Not reimbursed	Only in experimental setting	
Lithuania[1]	Not reimbursed	No	n.a.
Netherlands[1]	Not reimbursed	No	Not yet the standard of care and therefore not reimbursed, due to a lack of cost-effectiveness studies
Poland[1]	Not reimbursed	-	n.a.
Scotland[1]	Not reimbursed	Not routinely available	NICE guidelines published in August 2017. See this link: https://www.nice.org.uk/guidance/IPG590
Switzerland[1]	Not reimbursed	No information available	https://www.admin.ch/opc/de/classified-compilation/19950275/index.html
UK[1]	Reimbursed***** (as part of NHS England's Innovation and Technology Payment (ITP) 2019/2020 scheme).	Yes******	https://www.nice.org.uk/guidance/IPG590 https://www.nice.org.uk/guidance/indevelopment/gid-mt526 https://www.england.nhs.uk/publication/nhs-england-innovation-and-technology-payment-2019-to-2020-technical-notes/

[1] EUnetHTA partners from the respective countries provided the information.
*France, Reimbursement = no specific reimbursement of any spacer. But hospitals can buy it. So it is reimbursed as part of the DRG payment.
**Germany, Reimbursement= as part of the DRG payment in the in-hospital sector, no reimbursement in the out-of-hospital sector
***Italy, Reimbursement = the device is paid by the Italian NHS

****Italy, Implementation = the device is present in the Medical Device List managed at national level (Repertorio Dispositivi Medici)
*****UK, Reimbursement = no allocated tariff for reimbursement. However, SpaceOARTM is available to some providers under a zero-cost model as part of NHS England's Innovation and Technology Payment (ITP) 2019/2020 scheme. Providers can order SpaceOARTM directly from the company at zero cost. Participation is limited and agreed with the company before placing orders and all sites must agree to enter the company's Intent to Train programme.
******UK, Implementation = used in private practice and in selected patients as part of the NHS ITP 2019/20 programme.
Note: For reimbursement status of Boston Scientific, Biodegradable Rectum Spacers, see Table 3-2.

APPENDIX 3: CHECKLIST FOR POTENTIAL ETHICAL, ORGANIZATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

1	**Ethical**	
1.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes
	The intervention's invasiveness and the conditions of the insertion procedure should be clearly explained and time for questions and answers provided. Additional explanations on benefits and adverse events. The intervention should be available to those who are likely to benefit more (i.e. individuals with inflammatory bowel disease).	
1.2	Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	No
2	**Organizational**	
2.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organizational changes?	yes
	Insertion should be done before radiotherapy and by personnel trained in transperineal injections.	
2.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organizationally relevant?	yes
	The course and timing of the radiation procedure change (procedure becomes longer and more complicated). Spacer insertion should be performed before radiotherapy, and additional inconvenience for the patient, and additional organizational time to consider.	
3	**Social**	
3.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
4	**Legal**	
4.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
	There are no specific risks, but all risks should be explained to the patients before the procedure.	
4.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No

APPENDIX 4: MISCELLANEOUS

Table A12: Overview of individual ratings for the importance of the outcomes for decision-making

Outcome	Assessment team (AT), Patient (PP) Clinical experts (CE)							
EFFECTIVENESS	**AT**	**AT**	**AT**	**AT**	**PP**	**PP**	**CE**	**CE**
Rectal toxicity	8	8	9	9	nr	nr	8	9
Overall QoL	9	9	8	7	nr	nr	6	6
Sexual QoL	6	6	5	5	nr	nr	5	5
Bowel QoL	6	6	6	6	nr	nr	8	7
Overall survival	3	9	5	6	nr	nr	3	1
Urinary toxicity	6	8	7	9	nr	nr	7	3
Reduction in rectal radiation dose	8	?	7	3	nr	nr	8	6
Increase distance between rectum and prostate	6	3	6	3	nr	nr	6	6
PSA	5	3	5	6	nr	nr	3	1
Outcome SAFETY								
Mild to moderate adverse events (grade 1 to 2)	6	6	6	6	nr	nr	4	5
Severe to life-threatening adverse events (grade 3 to 4)	9	9	9	8	nr	nr	9	8
Deaths related to adverse events (grade 5)	9	9	5	9	nr	nr	9	6

PP contacted but none responded (nr).

Table A13: Documentation of queries to study authors in the assessment report

Study	Content of query	Reply received yes / no	Content of reply
Wolf 2015	▪ Request information about the 18 patients that are mentioned as having been tested in addition to the 78 included	No	▪
Saigal 2019	▪ Abstract found, inquire about full-text publication	No	▪
Loganathan 2019	▪ Abstract found, unable to find the author either by Research Gate or other means		▪
Kishi 2012	▪ Abstract found, inquiry about full-text publication	No	▪
Hamstra 2017	▪ Abstract found, inquiry about full-text publication	Yes	▪ Directed authors to full-text publication
	▪ Request to use graphical information	Yes	▪ Directed authors to publisher
	▪ Request PSA values at 3 years, and any other information for AEs available		▪
Cavanaugh 2018	▪ Abstract found, inquiry about full-text publication	Wrong address	▪

Cavanaugh 2016	▪ Abstract found, inquiry about full-text publication	Mistake in email address	▪
Baghwala 2019	▪ Abstract found, inquiry about full-text publication	no	▪

For the purpose of transparency, a separate document with comments on the 2nd draft assessment from external experts and the manufacturer(s) (fact check), as well as responses from the author, is available on the EUnetHTA website.