Health Technology Assessment (HTA) Decision Summary

The use of Barrigel and other rectal spacers when treating prostate cancer with radiation

SAPACT MEETING DATES	29th SAPACT Meeting (28 April 2023), 30th SAPACT Meeting (16 June 2023), 31st SAPACT meeting (18 August 2023)
APPLICATION #	2221
TECHNOLOGY	Barrigel - Radiotherapy protection spacer (Palette Life Sciences Australia Pty Ltd). Biodegradable hyaluronic acid of non-animal origin. *Other gel-based products are available locally and are included in this assessment as part of a broader review of this service:* SpaceOAR System - Radiotherapy protection spacer (Boston Scientific Pty Ltd). Absorbable hydrogel. DuraSeal Dural Sealant System - Dura mater sealant (Integra Neurosciences Pty Ltd). Absorbable polyethylene glycol.
TECHNOLOGY CLASSIFICATION	TGA class III
PATIENT INDICATION (TGA)	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. SpaceOAR 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 SpaceOAR System to reduce the radiation dose delivered to the anterior rectum. DuraSeal. The system is intended for use as an adjunct to standard methods of dural repair, such as sutures, to provide watertight closure.

SAPACT DECISION

☒ Restricted recommendation for clinical use subjected to implementation under audit conditions.

SAPACT Evidence Review Conclusions

Background

SAPACT received a request from SALHN for the use of Barrigel, a rectal spacer 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. In undertaking the review, SAPACT consulted with clinicians at the Royal Adelaide Hospital and also considered SpaceOAR, another rectal spacer available in Australia.

SAPACT recognised that the properties of these rectal spacers are different. Barrigel is injected as a gel and the product is reversible if needed. SpaceOAR is injected as a liquid but solidifies into a soft, but firm, hydrogel within 10 seconds.

Summary of evidence

Results from 2 randomised controlled trials (RCTs) were varied; however, the use of rectal spacers showed improvement in rectal toxicity and quality of life at up to 36 months. More severe toxic effects were less common. Other studies were varied in terms of study design, patient selection, type of radiotherapy and duration of follow-up.

Barrigel appears safe. SAPACT noted that while severe adverse events are possible for SpaceOAR, those reported in the literature were rare and transient in nature.

RCTs included patients with T1-T2 disease. Other studies report the use of rectal spacers in high-risk patients (T3 and T4). No issues were reported. SAPACT noted that the patient populations in the RCTs may not reflect how rectal spacers are commonly used in practice.

Costs

The costs of rectal spacers depend on whether they are able to be provided during a planned urology procedure (e.g. delivery of fiducial markers).

- Rectal spacer product costs are $1,731 per 9 or 10ml.
- Scenario 1: Spacer insertion at the same time of a planned trans-rectal ultrasound procedure (e.g placement of gold fiducial markers). Estimated additional theatre time of 10 minutes for both urologist and anaesthetist, with an additional cost of approximately $360 (including overheads). Estimated from activity-based costing in 2021-22, inflated to 2023-24 prices.
- Scenario 2: As an additional procedure. Estimated average cost of $2,871, based on national efficient price for M60B – Male Reproductive System Malignancy, Minor Complexity (2023-24 prices).

Most cost-effectiveness studies show that rectal spacers are not cost-effective. A careful selection of patients at highest risk of bleeding is likely to improve the cost-effectiveness of this product.

Local practice

SAPACT recognised that radiation oncology services are varied across SA Health. At SALHN, patients are commonly provided with gold fiducial markers. At the RAH, fiducial makers are less commonly used, other than for patients treated with stereotactic ablative body radiation therapy.

The total number of patients indicated for the use of rectal spacers across SA Health is uncertain. There may be up to, or over, an estimated 100 eligible patients per year at each site (SALHN and CALHN).

SAPACT Advisory Recommendations

SAPACT recognised that rectal toxic effects have a significant impact on certain patients and that rectal spacers can provide a benefit. Due to uncertainties in the clinical evidence and patient selection its use should be monitored.

Patient selection

- Patients with T1-T3b disease having radiation therapy.
- Rectal spacers should be used only in patients with localised or locally-advanced disease.
- Each patient should be considered on a case-by-case basis in terms of their bleeding risks and the potential benefits of rectal spacing. The risks, benefits and evidence related to rectal spacers should be explained to the patient, including any delay to the start of radiotherapy because of the procedure and the requirement for general anaesthetic.
- Radiation Oncologists and Urologists are required to discuss access to and use of rectal spacers at each site to ensure that appropriate and timely access to services is possible. In patients not otherwise having gold fiducial markers, rectal spacers need to be provided as a separate procedure which may have patient and system impacts.
- Factors associated with increased bleeding risks include:
    - High risk disease
    - Previous radiotherapy
    - Requirement to treat lymph nodes
    - Unfavourable patient anatomy
    - History of previous bleeding
    - Inflammatory bowel disease
    - Anticoagulation therapy
    - Androgen deprivation therapy
    - Diabetes
- Patients with no risks for bleeding, or where dose planning can reduce the rectal dose of radiation to an acceptable level, should not be provided with rectal spacers.
- Urologists should be appropriately trained in the use of rectal spacers.

Data collection and SAPACT update

Due to uncertainties around local use, patient numbers and impact on urology services and potential delays to radiotherapy the use of rectal spacers will be monitored for 2 years using the forms provided in Appendix A and Appendix B. Please provide your clinical reports to your LHN New Health Technology Committee which will be able to forward it to SAPACT on your behalf.

The literature review will be updated at 2 years to identify any new RCT evidence, long-term data and evidence related to high-risk patients (T3).

REGULATORY APPROVALS

☒ **Australia ARTG**:	☒ **US FDA**:	☒ **EU CE mark**:
339926 Barrigel - Radiotherapy protection spacer, 3ml, 21/07/2020 179172 SpaceOAR TM System - Radiotherapy protection spacer, 10ml, 14/01/2011 354010 SpaceOAR System - Radiotherapy protection spacer, nil variant, 1/02/2021 373630 SpaceOAR Vue System - Radiotherapy protection spacer, nil variant, 27/08/2021 233618 DuraSeal Dural Sealant System - Dura mater sealant, 1x5ml OR pack of 5, 10/02/2015 233759 DuraSeal Xact Sealant System - Dura mater sealant, 1x3mL and 5x3mL, 12/02/2015	Barrigel: 510(k) approval K220641, 26/05/2022 SpaceOAR: 21 CFR 892.5725, March 2015 DuraSeal: P080013, June 2009	Barrigel: *approved, date unclear* Space OAR: 2010 DuraSeal: 2005

QUALITY OF EVIDENCE

Quality of Evidence	A systematic literature search for best available HTA and policy evidence was conducted in Medline and 21 grey literature sources on 9 March 2023. The identified studies are varied in terms of study design, patient selection, type of radiotherapy and follow-up. One RCT of the use of Barrigel in patients receiving hypofractionated image-guided intensity modulated radiotherapy (IG-IMRT, 60 Gy in 20 fraction) was available (Madiados 2023).[1] This evidence is supplemented by: • Evidence from one available RCT on the use of SpaceOAR in patients treated with conventionally-fractionated IG-IMRT (79.2 Gy at 1.8 Gy per fraction) (Mariados 2015)[2] • Commentary on 6 non-randomised comparative studies on the use of Barrigel[3-8] • Evidence from systematic reviews of rectal spacers, with a focus on 2 recent HTA reports (NICE 2023, EUNetHTA 2020)[9, 10] • Evidence from 9 cost effectiveness analyses of rectal spacers[11-19] *The RCTs were funded by the product company, and authors declared conflicts including personal fees and shares*. Both RCTs were considered at 'some concerns' for overall risk of bias using the Cochrane RoB 2.0 tool, but were of reasonable design, conduct and reporting. In both RCTs patients were blinded, and adverse events were adjudicated by an independent committee masked to treatment randomization. However, patients were assessed for adverse events by a physician who was not blinded. Due to this the reporting of the adverse toxic rectal effects was at some risk of bias.

CLINICAL NEED	
Burden of Illness	Prostate cancer is the most diagnosed cancer in Australia. It is estimated that 1 in 6 males will be diagnosed by the time they are 85 years of age.[20] About 24,200 males were diagnosed with prostate cancer in 2022.[20, 21] In 2020, there were 3,568 deaths from prostate cancer in Australia.[22] Most patients present with local disease.[20] Based on Australian data from 2019, of 20,041 prostate cancer cases, 82% were stage 1 and 2 (early stage), 11% were stage 3, 4% were stage 4 (advanced) (3% were not able to be staged).[23] A range of treatment options are available including active surveillance, watchful waiting, surgery, radiation therapy including external beam radiation therapy (EBRT) or brachytherapy and androgen deprivation therapy.[20, 24] Management of prostate cancer is complex and depends on patient factors such as disease characteristics at diagnosis, personal preferences, existing comorbidities, and sometimes distance to treatment centres. Treatment options depending largely on grade and stage of disease at diagnosis.[24-26] Overall survival outcomes are similar across the therapeutic options.[26, 27] Radiotherapy has been shown to be an effective treatment option for Australian patients with local and locally advanced prostate cancer.[28-30] Radiotherapy includes EBRT which can be provided with conventional or hypofractionated dose (a larger daily dose >2Gy in fewer number of fractions, so the same overall therapeutic dose). EBRT includes image-guided, intensity modulated radiation therapy (IG-IMRT). The radiation dose can also be delivered using stereotactic radiotherapy (stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiation therapy (SBRT)) or brachytherapy (high-dose rate (HDR-BT) or low-dose rate (LDR-BT)). Local clinical advice is that SBRT is much more targeted and commonly used for patients with low risk prostate cancer. In terms of the overall dose of radiotherapy provided, local clinical advice was that all patients receive the same radiation dose, regardless of the prostate cancer risk classification. In addition to standard protocols, focal boost escalation has been found to improve biochemical disease-free survival by increasing the radiation delivered to the visible tumour (from fractions of 2.2 Gy to 2.7 Gy) with no difference in toxicity or quality of life.[31, 32] In South Australia, of men with non-metastatic prostate cancer treated with radiotherapy from 2005-15, 80% received EBRT and 20% brachytherapy.[33] Over time the modality of EBRT has changed with IMRT and VMAT (volumetric modulated arc therapy) becoming more common by 2015. Compared to conventional radiotherapy, hypofractionated radiotherapy has become more common in Australia and New Zealand and is associated with non-inferior outcomes.[34] In SA in 2019, a similar number of patients received each type of radiotherapy. **Side effects of radiotherapy** Side effects profiles differ between therapeutic options including higher rates of urinary incontinence and sexual dysfunction after surgery and of rectal bleeding after radiotherapy.[35] Recent data from South Australia shows that, compared to surgery at 12 months EBRT and BT showed improved sexual dysfunction and urinary incontinence but worse for urinary obstruction and bowel function.[36] The anterior rectal wall is particularly vulnerable to radiation-induced toxic side-effects due to its proximity to the prostate.[30] Rectal toxicity can include diarrhoea, bleeding, proctitis and ulceration of the rectal mucosa, haemorrhoids and pain.[9, 10, 37, 38] Effects may be acute (up to 3 months) or late (after 3 months) and may be at some time (e.g. 2 years) after radiotherapy (e.g. radiation proctitis). According to an Australian registry of 6,748 patients receiving radiotherapy, 8.3% of patients who received (moderately) hypofractionated EBRT (54- to 70-Gy total dose in 2.5 to 3.3 Gy/fraction) had moderate or big problem for 'bowel bother', and 9.8% had a moderate or big problem for 'urinary bother'. There were no clinically significant differences between hypofractionated and conventional radiotherapy.[34] Hypofractionated radiotherapy may be associated with less toxicity compared to conventionally fractionated radiotherapy.[37] The grade of rectal toxicity can be assessed using the Common Terminology Criteria for Adverse Events (CTCAE), or the modified Radiation Therapy Oncology Group (RTOG) criteria:[12] Grade 0: no symptom or complication was present; Grade 1: mild symptoms are present but no intervention is required; Grade 2: a moderate event affecting daily activities, intervention is required; Grade 3: a severe event that requires hospitalization; Grade 4: a life-threatening event; and Grade 5: death European and US guidelines recognise rectal toxicity as an effect of EBRT, but provide no detailed guidance beyond advice regarding treatment planning and patient information.[39-41] The rate of acute and late stage radiation proctitis of grade 3 or above is considered to be low (0 or 0.7%), with an overall incidence of gastrointestinal reactions of 4.4%.[42] A study of 231 patients treated with hypofractionated EBRT showed rates of grade ≥ 1, grade ≥ 2, and grade ≥ 3 late rectal bleeding of 23.8%, 16.9%, and 9.5%, respectively. Analyses showed that cirrhosis and anticoagulant use were associated with greater risk of grade ≥ 3 bleeding.[43] A separate study investigated a range of parameters in 149 patients who received EBRT (78Gy / 39 fractions) and found rectal dose to be significantly associated with rectal bleeding.[44] The overall rates of rectal bleeding in the cohort were 6% with grade 1 and 3.4% with grade 2. Other variables (e.g. age, use of anticoagulants, hormonal therapy) were not associated with

	increased risk of bleeding.
Need	The objective of rectal spacers is to reduce the radiation dose received by the rectum and to reduce the radiation-associated adverse events. To achieve this, rectal spacers temporarily increase the distance between the rectum and prostate to decrease rectal radiation dose and associated toxicity.[29] Rectal spacers include gel-based products (SpaceOAR, Barrigel, DuraSeal), also implantable balloons or human collagen.[5, 10, 45] The applicant has requested the use of Barrigel. The relevant products available locally are: • SpaceOAR, hydrogel, available since 2011, TGA approved for the purpose or rectal spacing • Barrigel, hyaluronic acid, available since 2020, TGA approved for the purpose or rectal spacing • DuraSeal, polyethylene glycol, used off-label for rectal spacing The injectable products are biodegradable. Over a few months these substances dissolve and are absorbed by the body. SpaceOAR is metabolised after 3-6 months.[29, 30] Barrigel begins to be absorbed after 3 months.[46] Barrigel is reversible with hyaluronidase and has been noted by local experts as being easier to use than SpaceOAR. **The procedure** The rectal spacer is commonly injected during the placement of gold fiducial markers. The injection is provided with trans-rectal ultrasound (TRUS) under, local or general anaesthesia, conscious sedation or spinal anaesthesia approximately one week before the start of radiotherapy.[10, 12] In published trials the choice of anaesthesia is commonly at the discretion of the physician.[47] Local clinical feedback suggests that in South Australia the procedure is undertaken under general anaesthesia. The gel is injected via a transperineal approach into the perirectal space between the Denonvilliers fascia and anterior rectal wall.[9, 12, 30, 47] Hydrodissection with saline can be used to separate the prostate and rectum but this is not always necessary.[10] Hyaluronic acid spacers are visible with TRUS. A volume of 9-12 ml is injected.[47] The Barrigel instructions for use advises that a volume of 3-10 ml creates a space of ≥10 mm, and that there is no experience with injecting more than 10 ml of the product.[46] The reported additional distance achieved between the prostate and rectum is 10-15 mm.[5, 45, 47] The median time for SpaceOAR injection has been reported as 4.1 (range 3.1 to 12.5) minutes.[48] The time for rectal spacer injection has been estimated by a local clinician as about 10 minutes if already set up for fiducial marker placement, with an allowance of a total theatre time of 30 minutes. According to Mariados 2023, although the spacer volume at 3 months decreased to a mean (SD) of 8.8 (1.8) ml, the mean prostate-rectum separation remained at 12.6 (SD 3.5) mm. Local clinical feedback from the applicant and a separate urologist indicates that Barrigel is easier to use than SpaceOAR. Barrigel has been reported for use in conjunction with a range of RT modalities in observational studies: • Hypofractionated IMRT (Mariados 2023, Boissier 2017, Chapet 2015, Chapet 2021, Chapet 2014) • Conventional IMRT/EBRT (Chapet 2013, Bjoreland 2023, Williams 2022) • Low dose-rate brachytherapy (Guimas 2016, Lin 2021, Prada 2009) • High dose-rate brachytherapy and IMRT (Wilder 2010, Wilder 2011) • Hypofractionated SBRT (Jmour 2020, Ozyigit 2020) • HDR brachytherapy (Prada 2012, Prada 2022) **Local activities** There have been no purchases of SpaceOAR or Barrigel through SA Health procurement. Local feedback suggests that rectal spacers are common for private patients. In CALHN and NAHLN rectal spacers (DuraSeal, due to its availability on the hospital formulary) are used very rarely in selected patents having brachytherapy treatment. DuraSeal is not used for patients receiving EBRT. Rectal spacers are not commonly used for patients undergoing EBRT, only for certain patients who receive SpaceOAR through self- or insurance-funding. CALHN clinicians have indicated an interest in the use of spacers for men receiving stereotactic radiotherapy, and for EBRT. At SALHN gold fiducial markers are commonly used (approximately 50% of patients currently have an associated procedure). At CALHN gold fiducial markers are used in all SBRT patients, but not used in other EBRT patients. EBRT patients have CBCT (Cone Beam Computed Tomography) with soft tissue match and do not receive gold fiducials It is recognised that the use of rectal spacers in the absence of gold fiducial marker placement would impact urologists, additional theatre time and costs.
CLINICAL BENEFIT	
Safety	• No procedural adverse events were reported for Barrigel in the RCT by Mariados 2023, or in any of the non-randomized comparative studies. • A recent systematic review of hydrogel spacers (SpaceOAR) reported a 97% (95%CI, 94.4%-98.8% [5 studies]) success rate with rectal spacer insertion and a low rate of procedural complication (0-10% of patients within the studies), which were mild and transient in nature.[30] • In the EUNetHTA review including SpaceOAR and Barrigel, there were no adverse events attributed to the hydrogel itself.[9] • According to the NICE review[10], there were 22 reports on the MAUDE database between January 2015 and March 2019, with

	surgical interventions required for perineal abscess (3), proctitis (1), rectal ulcer and haemorrhage (10, perirectal fistula (1), urinary tract infection and prostatic abscess (1), perineal abscess (1), severe urosepsis needing ICU admission (1). There was one death (the cause of death was unclear).
Effectiveness	**Rectal and genitourinary toxicity** RCT evidence was available for the use of rectal spacers for IG-IMRT Barrigel • From the RCT by Mariados 2023 with hypofractionated IG-IMRT, Barrigel was considered to be superior to control for grade 2 or higher GI toxic effect at 3 months (4 proctitis, 3 diarrhoea, 2 haemorrhoids, 1 rectal haemorrhage) (grade 0 effects, spacer population 114/136 (84.4%), control population 36/65 (55.4%), grade 1 spacer 17/136 (12.6%) control 20/65 (30.8%), grade 2 spacer 3/136 (2.2%) control 9/65 (13.8%), grade 3 spacer 1/136 (0.7%), control nil). • At 6 months all grade 2 or higher toxic events were resolved. All reported events were grade 0 (rectal spacer 12/136 (99.2%), control 57/57 (91.9%)) and grade 1 (rectal spacer 1/136 (0.8%), control 5/65 (8.1%), with no grade 2 or higher events reported. • There were no reported differences for genitourinary toxicity events. SpaceOAR • For SpaceOAR with conventional IG-IMRT, there were no differences in early (to 3 months) rectal toxicity (p=0.525) (Mariados 2015). For late toxicity (between 3 and 15 month visit) there was a significant reduction in rectal toxicity severity (p=0.044). However, there were few grade 2+ events reported (rectal spacer grade 1 events 145/148 (98%), grade 2 events 3/148 (2%); control grade 1 events 66/71 (93%), grade 2 events 4/71 (5.6%), grade 3 event (1/71, 1.4%)).[9, 10, 49-51] • There were no reported differences for early and late urinary toxicity (P=0.488 and 0.622 respectively). • At 36 months there were fewer grade 2 or greater rectal toxic effects in patients who received SpaceOAR (5.7% vs 0%, P=0.012). One grade 3 event was reported.[50] • There is one Australian non-randomised comparative study reporting on the use of Barrigel in patients receiving low dose-rate brachytherapy.[5] The use of rectal spacers did significantly reduce the rate of all GI toxicities (0% vs. 24%, p = 0.004 for acute GI toxicity; 4% vs. 33%, p = 0.003 for late GI toxicity). There was no difference in grade 2+ GI toxicities (none reported in either group). Across the evidence, more severe (grade 2 and above) clinical events are less common. Other relevant outcomes were also reported: **Quality of life** • The Barrigel RCT reported quality of life (QOL) as proportions of patients who had a minimal clinically important decline in QOL function (EPIC-26 QOL) at 3 and 6 months. There were no differences in EPIC-36 results for bowel (p=0.13 at 3 months, NR for 6 months), urinary (p=NR), sexual (p=NR) and hormonal (p=NR) parameters at 3 and 6 months. • One other study reported QOL for Barrigel. During the last week of radiotherapy, QOL (Expanded Prostate Cancer Index Composite Bowel Bother) was improved in patients treated with hyaluronan gel (n=30 v control, n=5) in a small non-randomised trial (p=0.03).[8] Patients were treated with combination high dose rate brachytherapy and IMRT. • The SpaceOAR RCT provided QOL data.[2, 9] Proportions of men experiencing minimally important differences (declines) in all three QOL summary domains at 36 months were 2.5% with SpaceOAR plus radiotherapy vs 20% in radiotherapy alone (p=0.002; difference relative to control 88%). Results suggest SpaceOAR plus radiotherapy may improve bowel QOL (p=0.002) over the entire follow-up period (36 months, 1 study, 140 participants; very low certainty of evidence) but the evidence is uncertain. Across the entire study period, results suggested that SpaceOAR may have little or no effect on urinary QOL (p=0.13) or sexual QOL (p=0.6) (1 study, 140 participants; very low certainty of evidence), but the evidence is very uncertain. **Radiation dosimetry** As noted by the EUNetHTA report, the dosimetry data are computed by the planning system and should be considered as a surrogate, rather than a clinical outcome.[9] Radiation dosimetry data is summarised below for information. • In the Barrigel RCT there was a mean reduction in rectum V54 (rectal volume receiving 54 Gy) of 85.0% (SD 20.9%). 131 of 133 (98.5%; 95%CI, 94.7%-99.8%) patients in the spacer group experienced a 25% or greater reduction in rectum V54 (p<0.001). • For SpaceOAR, as taken from the EUNetHTA report, RCT evidence showed a reduction in rectal dose compared with control. • The proportion of SpaceOAR plus radiotherapy patients who achieved ≥25% reduction in V70 was 97% (1 study, 220 participants; low certainty of evidence). When compared to control, SpaceOAR may result in a reduction in rV70 rectal dose to the rectum (p<0.0001).[9] **Placement success** • Placement success was not reported in the Barrigel RCT or comparative studies. No procedural adverse events were reported in any of these studies. • For SpaceOAR, spacer placement success in the spacer group (defined as hydrogel present in the perirectal space) was reported as 99%. Urologists and oncologists rated spacer application as 'easy' and 'very easy' 99% of the time.[10] **Long-term follow-up** Follow-up from the RCTs is described above. For Barrigel, the maximal follow-up was 6 months; for SpaceOAR the maximal follow-up

	was 36 months. Barrigel For Barrigel non-randomised comparative studies, 2 studies provided long-term follow-up: • Lin 2021 (N=70) is an Australian study of LDR brachytherapy with a median follow-up of 23.5 (IQR = 20.75) months. There were significantly less grade 1 acute and late GI toxicities in patients who had received Barrigel. There were no reported acute or late grade 2 or above GI toxicities in any patient. • Prada 2009 (N=69) had a follow-up of a median of 26 (range 21-39) months for patients treated with brachytherapy. Patients with Barrigel had significantly lower incidence of mucosal damage at endoscopic examinations (5% vs. 36%, p=0.002) and no macroscopic rectal bleeding (0% vs. 12% [4 of 33], p=0.047). There was no reported grade 3 or greater bleeding in any patient. • Other studies reported short-term follow-up to 3 or 5 months or provided solely dosimetry data. For Barrigel single-arm studies, two recent studies provided longer-term follow-up: • Bjoreland 2023 (N=81) followed up to 5 years and reported both observed and patient-reported rectal toxicity. The cumulative late grade ≥ 2 GI toxicity at 5 years was 5% and the proportion of patient-reported moderate or severe overall bowel problems at 5 years follow-up was 12%. Cumulative late grade ≥ 2 GU toxicity at 5 years was 12% and moderate or severe overall urinary problems at 5 years were 10%. • Chapet 2021 (N=36) followed-up to a range of 3-36 months. There were no grade 3 or 4 events. At 36 months there were 7% (2/30) grade 1 events (there were no grade 2 events). At between 3 and 36 months there were 32% (11/34) grade 1 events and 12% (4/34) grade 2 events. SpaceOAR For SpaceOAR, long-term follow-up was reported in the NICE report, with data taken from a recent systematic review.[10, 30] As taken from the NICE report "pooled results from 6 studies showed that the risk of early grade 2 or higher rectal toxic effects (at 3 months follow up) was comparable and not statistically significantly different between the hydrogel spacer and control groups (5% versus 4%; RR, 0.82; 95% CI, 0.52 to 1.28; p=0.38). However, in a pooled analysis of 4 studies, at late follow up (median, 38 months; range, 28 to 60 months) the risk of grade 2 or higher rectal toxic effects was lower in the hydrogel spacer group compared to controls (2% versus 6%; RR, 0.23; 95% CI, 0.06 to 0.99; p=0.05)." For SpaceOAR QoL long-term follow-up, the results were as presented above from RCT evidence. Therefore, rectal spacers do show some improvement at longer-term follow-up in terms of rectal toxicity and QoL, however, the overall rates of adverse events in patients with no rectal spacer appears low. In the longest follow-up case series, reported rectal toxicity in patients with Barrigel was approximately 10%.
SUITABILITY OF PATIENT GROUP	
Suitability of Patient Group	**Proposed patient group:** Patients with T1-T3b disease who are having radiation therapy. **Number of patients per year:** 51-75 patients (SALHN). At the RAH, the total number of CALHN and NALHN radiotherapy patients per year is 250-350 (including brachytherapy and post-prostatectomy or recurrent or metastatic disease): • Of these approximately 30-40 brachytherapy patients would receive rectal spacer (DuraSeal) at the same time as seed implant • All SBRT patients (approximately 15) have gold fiducial marker implants (transperioneally). • Not all patients would choose to have rectal spacers due to the risks and requirement of an additional procedure. However, significant engagement from urology would be needed to provide this service to patients • In total, an estimated 100+ patients may benefit from rectal spacers **Patient selection** The Barrigel RCT by Mariados 2023 included patients with biopsy-proven, T1 to T2 prostate cancer with a Gleason score 7 or less and prostate-specific antigen level of 20 ng/mL or less. Patients were allowed androgen deprivation therapy. Patients with prostate volume less than 15 ml or greater than 90 ml were excluded. Baseline characteristics of the rectal spacer population in the Barrigel RCT were: • Gleason score 6 (25.7%); 7 (74.3%) • T1a-T1c (79.4%), T2a-T2c (20.5%) • Mean PSA level 6.7 ng/ml (SD 3.5, range 1.0-19.5) • Androgen deprivation therapy (68.4%) **High-risk patients** Published trials have commonly included broad populations defined as early stage prostate cancer or low or intermediate risk patients with localised or locally advanced prostate cancer.[10] Williams 2022 is an Australian study which reported the use of Barrigel in 102

	patients with clinical stage T1c-3b prostate cancer who underwent general anaesthesia for fiducial marker insertion and injection of rectal spacer into the perirectal space before EBRT.[52] 17.5% patients were cT3 (15.6% cT3a and 2% cT3b, and 28.4% were considered unfavourable intermediate, 37.3% high risk. 70.6% patients were on ADT. Dosimetry data but no clinical data was reported, and no sub-populations were reported separately. No adverse events were reported during the brief (2 week) follow-up period, and the separation was approximately 10mm in all patients. There was a reported reduction in rectal dose. A formal evaluation of literature pertaining to the use of SpaceOAR in patients with high-risk prostate cancer was not undertaken. However, evidence regarding T3 patients is provided in the EUNetHTA and NICE assessments and 5 recent (published since 2020) systematic reviews.[9, 10, 29, 30, 48, 53, 54] 7 non-randomised comparative studies included T1-T3 patients (follow-up 9.5 to 60 months), and one included T1-T4 patients treated with combination LDBT in combination with EBRT (follow-up not reported).[10] No adverse events were reported. The systematic reviews do not report any issues with the injection of rectal spacers in patient with high-risk prostate cancer. Some studies have indicated patient populations which are at greater risk of rectal toxicity, and therefore may have increased benefit from rectal spacers compared to the routine adoption for all patients: • Mariados 2023 notes that higher rates were seen in trials which had high use of androgen deprivation therapy[47] • A Cancer Care Ontario report commented that appropriate patient selection was not yet defined but that the technology may be best used in patients in whom standard rectal dose-volume criteria are not met; those treated with ultrahypofractionated RT; and those at higher baseline risk of rectal toxicity.[45] • Payne 2021 reported in a consensus of experts from the UK that because of funding limitations, patients needed to be prioritised for spacer use. A higher benefit of spacers can be expected in patients on anticoagulation and in patients with diabetes or inflammatory bowel disease, and in patients receiving ultrahypofractionated regimens.[55] • An Australian cost-effectiveness study identified that hydrogel spacers are more cost-effective if patients are better selected. The targeted patient selection was modelled using a predictive model.[15] • Hutchinson 2016 identified that the cost-effectiveness of a hydrogel rectal spacer varied; it was cost-effective for high-dose SBRT, but not cost-effective for conventional EBRT.[14] • Brooks 2019 undertook two different scenarios based on the assumed effects of rectal spacers. Spacers were more cost-effective when greater benefits were modelled in the analysis.[11] • In a small study of individual patient outcomes, Van Wijk 2017 identified that hydrogel spacers were cost effective for some but not all patients. Modelling the predicted effect of rectal spacers using previous CT images helped to identify patients at greatest risk of rectal effects.[18] No other guidelines were identified.
FINANCIAL CONSIDERATIONS	
Device costs	Barrigel and SpaceOAR are included on the Prosthesis List (Dec 2022): • Barrigel, 3ml, $844 • Barrigel, 9ml, $1,731 ($173 per 1ml) • SpaceOAR, 10ml, $1,731 • SpaceOAR VUE, 10ml, $1,731 ($173 per 1ml) DuraSeal is not included on the Prosthesis List. DuraSeal is available through SA Health Oracle • 1 carton of DuraSeal has 5 x 5ml vials in it. Each carton of DuraSeal costs $[redacted] ($[redacted] per ml) Hydrogel spacer costs in a recent Australian cost effectiveness study were estimated at $1,650.00 (hospital records).[15] No additional procedure costs were included in this analysis.
Value for Money	A number of cost-effectiveness evaluations were identified.[11-16] Where reported, all analyses were for the use of hydrogel spacers (SpaceOAR). Cost effectiveness analyses variously consider the use of rectal spacer as part of the existing procedure (gold fiducial marker placement) or as a separate independent procedure. In all studies the use of rectal spacer is overall more costly, although the use of rectal spacers was less costly for patients treated with high dose SBRT.[14] In some circumstances authors state that the use of rectal spacers are cost-effective, based on a certain threshold. One Australian cost-effectiveness study in a public hospital setting the ICER was $63,000 per QALY (all patients) but lower ($20,000) in selected patients.[15] Overall the studies show that the use of rectal spacers is more costly than standard care (i.e. no rectal spacer) and results vary based on the assumptions and different scenarios. The cost and service impact of rectal spacers will vary depending on whether the injection can be provided as part of an existing procedure (placement of gold fiducial markers), and the number of vials used.
Australian and International Funding Approvals	The Commonwealth Medical Services Advisory Committee (MSAC) has not investigated any rectal spacer product. HealthPACT reviewed rectal spacers in 2013.[38] At this time the use of rectal spacers (specifically SpaceOAR) was in limited use in Australia. At this time HealthPACT recognised that a small evidence base provided support for the safety and effectiveness of the modality. HealthPACT recommended monitoring the technology until the publication of an ongoing RCT (NCT01538628). The pivotal RCT and associated follow-up publications are included in recent systematic reviews.[2]

	Interstate experiences A request was sent to state and territory colleagues. No responses were provided. This may be as the use of rectal spacers is decided on a local or hospital basis. Overseas experiences UK National Institute for Health and Care Excellence (NICE) Guidance 2023: NICE recommended that[56] • Evidence on the safety and efficacy of biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer is limited in quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. NICE committee comments: • The committee was informed that there may be groups of patients who derive particular benefit from this procedure because they are at increased risk of developing severe symptoms of rectal toxicity after radiotherapy. This includes those with inflammatory bowel disease or on anticoagulation treatment. However, there was no published evidence to indicate which groups of patients benefited from this procedure. • The committee was informed that the incidence of rectal toxicity after radiotherapy has decreased over time with improvements in radiotherapy techniques. • The committee noted that there was a considerable amount of information from unpublished audits. NICE encourages publication of such data to allow it to be considered in future updates of this guidance. • The committee was informed that some spacers are radio-opaque and can be seen on CT, and these may reduce the need for MRI scanning These NICE recommendations are a change to those published by NICE in 2017, which were: • Current evidence on the safety and efficacy of insertion of a biodegradable spacer to reduce rectal toxicity during radiotherapy for prostate cancer is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit. • The procedure should only be done by clinicians with training in, and experience of, transperineal interventional procedures. The recent EUNetHTA review (which included SpaceOAR and Barrigel) concluded that:[9] • 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.
FEASIBILITY OF ADOPTION	
Organizational Feasibility	This product requires timely access to urologists, anaesthetists and theatre time. This technology may be used provided that standard arrangements are in place for funding, clinical governance, consent and audit by the LHN(s).
Credentialing and Competency	The procedure should only be provided by clinicians who are experienced at TRUS.
CONSISTENCY WITH EXPECTED SOCIETAL/ ETHICAL/ LEGAL VALUES	
Values	Consistent with expected societal, ethical and legal values at this time. The additional time and organizational requirements to provide this therapy should be considered. Any impact of the procedure on delays in radiotherapy should be understood and explained to each patient. The requirement of the product should be considered and discussed with each patient. The invasiveness of the procedure, the potential benefits and adverse events should be explained.
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