Health Policy Advisory Committee on Technology

Technology Brief: Update

Inert liquid-to-solid gels for prostate-rectum separation during prostate radiation therapy

February 2013

HealthPACT
emerging health technology
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This brief was prepared by Dr Ann Scott, Dr. Merricc Edgar-Hughes and Dean Forel from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).
Register ID: WP 124

Name of Technology: Inert liquid-to-solid gels for prostate-rectum separation during prostate radiation therapy

Purpose and target group: Various inert substances injected between the rectum and prostate can maintain a space during prostate cancer radiation therapy to protect rectal tissue from radiation side effects

Stage of development in Australia:
- ☐ Yet to emerge
- ☐ Experimental
- ☐ Investigational
- ☒ Nearly established
- ☐ Established
- ☐ Established but changed indication or modification of technique
- ☐ Should be taken out of use

Australian Therapeutic Goods Administration approval:
- ☒ Yes
- ☐ No
- ☐ Not applicable

ARTG number (s): 179172

International utilisation:

<table>
<thead>
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<th>Country</th>
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<th>Limited use</th>
<th>Widely diffused</th>
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Since the inclusion of SpaceOAR™ System on the ARTG, there is limited use of this product in New South Wales and Victoria.
2013 Safety and effectiveness issues
Two case series studies (level IV intervention evidence), including a total of 69 men, were eligible for inclusion in this update.
Hatiboglu et al
This prospective case series study, undertaken at four centres in the European Union between July 2010 and January 2011, examined the use of the SpaceOAR™ System (Augmenix, Inc., Waltham, MA, USA) in 29 men with low- or intermediate-risk prostate cancer (T1c to T2c stage) and a prostate volume of less than 80 mL (median 58 mL). The men, whose average age was 67 years, had Gleason scores of between six (48%) and seven (52%). Over half of the patients (59%) had a serum prostate-specific antigen level of between 4 ng/mL and 10 ng/mL. Men were excluded from the study if they had metastatic disease; a history of prostate, rectal or gastrointestinal surgery; previous radiotherapy to the pelvis; or active inflammatory bowel disease.
The gel (10 mL) was injected trans-perineally between Denonvilliers’ fascia and the rectal wall under trans-rectal ultrasound guidance using a hydro-dissection technique. On average, the procedure was completed in 16 (standard deviation [SD] 7.8) minutes, with a mean injection time of six (SD 3.2) minutes. Prophylactic antibiotics were prescribed at the discretion of the physician. Within 19 days of injection, the patients began intensity-modulated radiation therapy at a dose of 78 Gy delivered over an 8-week period. Computed tomography or magnetic resonance imaging scans taken at baseline and approximately one week, three months and six months after gel insertion, were reviewed by an independent radiation oncologist.
The gel was implanted successfully in all patients under local, spinal or light general anaesthesia in an outpatient setting. None of the patients experienced adverse events. The mean prostate-rectum space created by the gel was 9.9 (SD 5.92) mm at one week after injection, 10.5 (SD 4.33) mm at three months after injection and 1.7 (SD 2.94) mm at six months after injection. The amount of space created was not affected by prostate size. The mean rectal volume receiving a radiation dose that exceeded 70 Gy (V70) was reduced by 60.6 per cent after implanting the gel, from 14.6 per cent to 5.8 per cent. Functional success, defined as the formation of a space between the posterior prostatic capsule and the anterior rectal wall of at least 7.5 mm, was achieved in 28 of the 29 patients (96.6%). Of the 27 patients with evaluable planning simulations, 26 (96.3%) achieved clinical success (at least a 25% reduction in rectal V70). One patient who did not meet the criterion for functional success did achieve clinical success, with a reduction in rectal V70 of 49 per cent. In the patient who did not achieve clinical success, the mid-gland distance increased from 2.7 mm
to 15.2 mm, but this likely did not affect the V70 because the rectal volume was much larger before than after gel injection (289 mL versus 189 mL).

Prada et al\(^2\)

This prospective case series study examined 40 consecutive men with low- or intermediate-risk prostatic adenocarcinoma (T1c to T2c stage) who were treated with brachytherapy between April 2008 and January 2010. The median age was 71 (range 59 to 79) years. Two men (5%) had Gleason scores of seven, while the remainder had scores of six or less. The median prostatic volume was 42 (range 16 to 73) mL at baseline, and over three quarters (80%) of the men had a serum prostate-specific antigen level lower than 10.1 ng/mL.

Hyaluronic acid was injected trans-perineally into the perirectal fat of the patients, who then received 19 Gy high-dose-rate brachytherapy in one fraction. All patients were discharged from hospital on the day of treatment, within eight hours of the procedure. No intra-operative or peri-operative complications occurred. Asymptomatic acute anal mucositis grade 1 occurred in five patients (12.5%) one week after injection, but this had resolved by six months in all patients. Anal pain, rectal bleeding, diarrhoea, anal ulcer or recto-urethral fistula did not occur in any patients during the median follow-up period of 19 (range 8 to 32) months.

The median level of serum prostate-specific antigen was 1.2 (range 0 to 5) ng/mL after treatment. The overall Kaplan-Meier survival was 98 per cent (standard deviation 2%) at 32 months, while the actuarial biochemical control was 100 per cent and 88 per cent for the low- and intermediate-risk groups (\(p=0.06\)), respectively, over the same time period.

2013 Cost impact

No economic studies were identified by the literature search. The price of the SpaceOAR\(^\text{TM}\) System provided by the Australian distributor is approximately $2000. The local Australian distributor has a reimbursement application lodged with the Prostheses List Advisory Committee.\(^3\)

2013 Ethical, cultural or religious considerations

No issues were identified from the retrieved material.
**2013 Other issues**

A search of the Australian New Zealand Clinical Trials Registry (ANZCTR) identified one prospectively registered trial. The trial registration details indicate that the first patient enrolment was expected to begin in June of 2012. The trial is currently listed as not yet recruiting. The SpaceOAR™ System is not specifically mentioned in the trial registration details; however, the local distributor and trial sponsor, MD Solutions Australasia, of the SpaceOAR™ has confirmed that it is a trial using SpaceOAR™ System.³ The trial will assess the feasibility of using polyethylene glycol hydrogel to increase prostate-rectum separation and its impact on rectal dose during radiation therapy. The trial has a target sample size of 40, will enrol adult males with localised prostate cancer fit for prostate brachytherapy and will use historical data from a prostate cancer database as the control. No expected completion date is available.

A search of the clinical trial databases identified two ongoing clinical trials.

Augmenix, Inc., is sponsoring a multicentre, randomised controlled trial in the United States (NCT01538628) that will assess the safety and efficacy of the SpaceOAR™ System up to six months after injection compared with no treatment. Recruitment of 222 adult men with localised stage T1 or T2 prostate cancer is underway and the study is expected to finish in May 2014.

The University of Oulu in Finland is sponsoring a case series study (NCT01601691) on the safety and efficacy of DuraSeal™ (Covidien AG, Zurich, Switzerland), a polyethylene glycol hydrogel used to seal the dural membrane during spine surgery. The trial is currently recruiting, by invitation, 10 men aged between 50 and 76 years who are due to undergo low-dose brachytherapy for prostate cancer. The trial, which will provide results up to 12 weeks post-injection, is expected to be completed in March 2013.

A planning study by Pinkawa et al.⁴ evaluated the theoretical impact of using 10 mL of SpaceOAR System™ gel in 18 patients (mean age 71 years) with prostate cancer who had a serum prostate-specific antigen level of less than 20 ng/mL and a Gleason score lower than four. The gel was administered trans-perineally under trans-rectal ultrasound guidance using a hydro-dissection technique. Three-dimensional conformal radiotherapy and intensity-modulated radiotherapy treatment plans delivering a theoretical radiation dose of 78 Gy were compared using computed tomography imaging. The spacer gel increased the distance between the prostate and the anterior rectal wall by at least 6.6 mm in 16 (89%) men (mean change 8 mm in the medial plane, p<0.01). Models of the treatment plans, comparing pre-spacer and post-spacer treatment, estimated that the rectal radiation doses and volumes would be significantly lower after gel injection (p<0.01 for all comparisons). Thus, the
mean normal tissue complication probability for severe proctitis, necrosis, fistula or rectal bleeding could be reduced by at least 50 per cent, irrespective of the radiation treatment technique used. However, as this was a planning study, no radiation doses were actually administered to the patients.

2013 Summary of findings
Since the production of the original report, the SpaceOAR™ System has become commercially available in Australia but has had limited uptake.

The two level IV intervention studies, which contributed a relatively small total population of 69 patients, showed that the injection of either hyaluronic acid or the SpaceOAR™ System gel is a potentially safe and effective means of increasing the distance between the posterior prostatic capsule and the anterior rectal wall in men undergoing radiation therapy for low- to intermediate-risk prostate cancer. However, while both studies reported on the anatomical effects of spacer gel injection, only one provided data on the potential clinical impact of these gels in terms of reducing the gastrointestinal toxicity of radiation therapy. While gastrointestinal morbidity was mild and occurred in only five of the 40 patients being treated with brachytherapy after gel insertion, it is unclear whether this was due to the presence of the gel or the innovative high-dose-rate brachytherapy monotherapy protocol that was also being investigated. Comparative data are essential to ascertain how effective the insertion of a spacer gel between the rectum and the prostate is in protecting rectal tissue from the adverse effects of radiation therapy. The results of the randomised controlled trial on the SpaceOAR™ System, which is scheduled to end in May 2014, are likely to be an important addition to the evidence base regarding the effectiveness of this simple and apparently safe protective strategy. There is currently one registered Australian trial underway in New South Wales but there is no completion date scheduled.

2013 HealthPACT assessment
This 2013 update of the evidence base available for the use of inert liquid-to-solid gels for prostate-rectum separation during prostate radiation therapy provides continued support for the safety and effectiveness of this modality. Although the evidence base remains small, injection of hyaluronic acid or the SpaceOAR™ System gel appears to successfully increase the distance between the posterior prostatic capsule and the anterior rectal wall which resulted in reduced gastrointestinal toxicity in the one study reporting this outcome. Based on this, and the claim that inert liquid-to-solid gels have the potential to reduce the incidence of severe proctitis, necrosis, fistula or rectal bleeding by 50%, this technology will be
monitored for a further 24 months; during which time the results of the RCT currently underway will become available.

**2013 Number of studies included**

All evidence included for assessment in this Technology Brief has been assessed according to the revised National Health and Medical Research Council levels of evidence. A document summarising these levels may be accessed via the following link on the HealthPACT web site.

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<thead>
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<tr>
<td>Total number of level IV Intervention evidence studies</td>
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</table>

**2013 References**


**Prioritising Summary**

**Register ID**  S000125

**Name of Technology**  Inert liquid-to-solid gels for prostate-rectum separation during prostate radiation therapy

**Purpose and Target Group**  Various inert substances injected between the rectum and prostate can maintain a space during prostate cancer radiation therapy in order to protect rectal tissue from radiation side effects

**Stage of Development (In Australia)**

- [✓] Yet to emerge
- [ ] Experimental
- [ ] Investigational
- [ ] Nearly established
- [ ] Established
- [ ] Established but changed indication or modification of technique
- [ ] Should be taken out of use

**Australian Therapeutic Goods Administration Approval**

- [ ] Yes  ARTG number  NA
- [✓] No
- [ ] Not applicable

**International Utilisation**

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<td>Spain</td>
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**Impact Summary**

Augmenix Inc. (Waltham, Massachusetts) has developed a synthetic liquid hydrogel (SpaceOAR™) that solidifies in the body to form an absorbable mass. After injection between the prostate and rectum before prostate cancer radiotherapy, it protects the rectal wall by maintaining a space between the prostate and rectum. It then gradually liquefies and is absorbed. Studies located for this summary did not specifically employ SpaceOAR but rather a similar (but naturally-derived) cross-linked hyaluronate gel marketed at that time by Genzyme Inc. (Cambridge, Massachusetts), or other forms of hyaluronic acid used primarily for aesthetic procedures of the face.

**Background**

Inert gels for prostate-rectum separation during prostate radiation therapy

November 2010
Prostate cancer is the most common cancer in men, accounting for 25% of all cancers; most (74%) arise posteriorly in the peripheral zone of the gland and therefore adjacent to the rectum (Wilder et al 2010a). Treatment of early prostate cancer often employs transperineal ultrasound-guided brachytherapy using permanent implants of I-125, followed by a course of radiotherapy; however, rectal toxicity including diarrhoea and bleeding can complicate therapy in up to 20% of cases (Prada et al 2009). A dilemma therefore arises in the balance between radiation dose and rectal adverse effects.

Researchers have tried various technologies to protect rectal tissue when radiation is being delivered to the prostate. One such paradigm is the use of an inert protective substance such as hyaluronic acid, hyaluronan gel or, most recently, synthetic hydrogel (SpaceOAR). These substances can be injected as liquids into the anterior perirectal fat. They then solidify, forming small protective masses or barriers (Figure 1). Over a few months they dissolve and are absorbed by the body. In particular, the SpaceOAR System (currently the only commercially available product for this purpose) is a synthetic hydrogel composed of approximately 90% water, with the remaining solids being cross-linked polyethylene glycol (PEG).

Figure 1: Illustration of the positioning of SpaceOAR
(Source: http://www.augmenix.com/prostate-radiation - used with permission from Augmenix)

**SpaceOAR hydrogel moves the rectum away from the high dose radiation field**

<table>
<thead>
<tr>
<th>Without SpaceOAR</th>
<th>With SpaceOAR</th>
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<tr>
<td><strong>High Dose</strong></td>
<td><strong>High Dose</strong></td>
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<tr>
<td><strong>Low Dose</strong></td>
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<tr>
<td><strong>Prostate</strong></td>
<td><strong>Prostate</strong></td>
</tr>
<tr>
<td><strong>Rectal Wall</strong></td>
<td><strong>Rectal Wall</strong></td>
</tr>
</tbody>
</table>

**CLINICAL NEED AND BURDEN OF DISEASE**
Each year in Australia approximately 20,000 new cases of prostate cancer are diagnosed and close to 3,300 men die of the disease; this equates to 32 new diagnoses of prostate cancer per day and one death every three hours (Prostate Cancer.
Inert gels for prostate-rectum separation during prostate radiation therapy
November 2010


DIFFUSION
With regard to SpaceOAR, which appears to be the only specific product currently available for prostate-rectum separation, approval by the Therapeutic Goods Administration (TGA) or the United States (US) Food and Drug Administration (FDA) had not occurred (at the time of writing). The product has received CE mark approval according to a news release in August 2010 (Medical News Today 2010).

An FDA Investigational Drug Exemption was required to allow the Phase I prospective study of Wilder et al (2010a) to take place, which was limited to 10 patients. As well as this, in the studies by Wilder et al, Hylaform, a Genzyme product (Allergen in Australia) described as a ‘Tissue reconstructive material, biological’ was used. This material was approved in Australia in July 2008 (Class III, ARTG number 153625) for ‘the correction of wrinkle, folds, scars of the face by injection’ (ARTG 2008).

COMPARATORS
Researchers in Israel have developed an implantable biodegradable balloon (35 mm x 10-20 mm) to protect the rectal wall during radiotherapy (Wilder et al 2010a, Wilder et al 2010b). Thus far limited to animal testing, exploration in patients with prostate cancer is planned. However, in comparison with the use of inert gels, disadvantages include the need for a larger dilator and sheath for insertion (versus a 17-gauge needle); the need for a minor surgical procedure for device removal; theoretical complications of foreign body reactions, rectal ulceration, and fistula formation; and lack of billing codes in the US for balloon placement and removal, thus discouraging device development in that country (Wilder et al 2010a, Wilder et al 2010b).

SAFETY AND EFFECTIVENESS ISSUES
Four small studies were eligible for inclusion in the review (Table 1). One included a historical control group (Wilder et al 2010a), a second included a very small contemporary control group (n=5) (Wilder et al 2010b), the third claimed to be randomised but there was no description of randomisation methods or further reference to this design (Prada et al 2009), and the fourth was a case series (Prada et al 2007).
Table 1: Studies on cross-linked hyaluronan gel for prostate-rectum separation

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<td>Case series w/ historical controls</td>
<td>Median 3 months</td>
<td>Acute rectal toxicity</td>
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<td>Case series w/ contemporary controls</td>
<td>Median 5 months (range 5-12)</td>
<td>Quality of life</td>
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<td>01/05 to 07/06</td>
<td>n=36; n=33</td>
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<td>Pseudo-randomised controlled trial</td>
<td>Median 26 months (range 21-39)</td>
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<td>Median 13 months (range 9-22)</td>
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Study profiles

In the study by Wilder et al (2010a) researchers at the Cancer Center of Irvine in California conducted a Phase I, prospective, open-label study in patients with early stage prostate cancer (n=10). The aim was to see whether cross-linked hyaluronan gel could reduce the mean rectal dose and acute rectal toxicity of radiotherapy. The gel employed was Hylaform (Genzyme Corp., Cambridge, MA), a hydrogel manufactured from rooster combs which are composed mainly of hyaluronic acid. Enrolled were men (aged 66-83 years) with early stage, node negative prostate cancer with prostate volume <50 cc and prostate specific antigen (PSA) ≤ 30 ng/ml (clinicaltrials.gov, 2009). Under general or spinal anaesthesia, the men received a 9 cc transperineal injection of Hylaform gel divided among three doses in slightly different peri-prostate locations on Day 1 and again a week later in order to increase the separation between the prostate and rectum to 8-18 mm. The men underwent brachytherapy (to 2200 cGy) on each of these days, followed by intensity-modulated radiation therapy (IMRT) to 5040 cGy in 28 daily fractions over 5.5 weeks, beginning 1 to 4 days after brachytherapy. Magnetic resonance imaging (MRI) can clearly visualise the gel (unlike computed tomography [CT]) and was used for monitoring. Results for these 10 patients were compared with historical results for 239 men who received the same treatment without use of gel.

In another study by Wilder et al (2010b), the same researchers conducted a larger Phase I study focussed on quality of life (QOL). Surgical treatment was as described in Wilder et al (2010a) but this time 35 patients were enrolled, five serving as controls and 30 receiving cross-linked hyaluronan gel before brachytherapy and IMRT.1 To assess QOL, all 35 patients completed Expanded Prostate Cancer Index Composite (EPIC) self-assessment questionnaires (developed at the University of Michigan) before treatment and at the end of radiotherapy. The validated EPIC questionnaire included 50 questions divided among urinary, bowel, sexual and hormonal categories. Within the bowel domain, questions focus on symptom severity and bowel bother (BB).

1 As study enrolment periods between the two studies overlap, it is not clear whether the 10 patients in Wilder et al (2010a) were included in this larger study.
Prada et al (2009) described as randomised (no randomisation details provided), 69 consecutive outpatients with low-risk (60%) and intermediate-risk (40%) prostate cancer who were to receive low-dose-rate brachytherapy treatment and were enrolled in one of two groups. The intervention group (n=36) received a 6-8 cc of hyaluronic acid (HA; facial filler Restylane®, Sweden) injected into the anterior perirectal fat after the implantation of permanent brachytherapy seeds, whereas the controls (n=33) did not. Patient groups were similar with respect to age, tumour stage, pre-treatment PSA, risk status and prostate gland volume. Outcome was degree of rectal mucosal damage as assessed via endoscopy a mean of 18 months post-therapy by an endoscopist who was blinded to treatment group.

Finally, Prada et al (2007) were the first to publish results of the use of injected HA into the anterior perirectal fat to increase the space between the prostate and the rectal wall, and thereby protect the rectum from the complications of radiation therapy. The enrolled patients (mean age 67 years, range 55-77) were poorly described but appear to have had more advanced prostate cancer than those in the three studies described above, e.g. 64% had Stage ≥ 3a disease with median PSA 21 ng/mL. Patients received external beam radiotherapy with high-dose-rate brachytherapy boosts over a five-week period with a 3 cc to 7 cc HA injection given under transrectal ultrasound guidance during week three. Outcomes included duration of the HA stability, mean distance between prostate and rectum, and median measured rectal dose of radiation.

Safety

All studies reported that there were no adverse events or safety concerns. Theoretical adverse events were infection (antibiotics were given prophylactically); allergic reactions such as itching; injection site reactions, e.g. tenderness, pain, bleeding, bruising, redness, discoloration, granuloma and keloid formation; tenesmus, rectal pressure, or a sensation of rectal filling; and systemic embolisation if the gel was injected into a blood vessel rather than into fat (clinicaltrials.gov 2009).

Efficacy

The small Phase I study (limited to 10 patients by the FDA) by Wilder et al (2010a) focussed on rectal toxicity in the intervention group versus controls at the same cancer clinic, using the National Cancer Institute Common Terminology for Adverse Events v3.0 grading scheme. At median follow-up of three months, there was a 0% incidence of rectal toxicity versus 30% in historical controls ($P=0.04$). The mean rectal radiation dose at the start of IMRT in the intervention group (a strong predictor of rectal toxicity) was $73\pm13$ cGy versus $106\pm20$ eGy in the control group ($P=0.005$).

The focus of the second study by Wilder et al (2010b) was QOL scores, particularly the section on the EPIC questionnaire related to bowel function. Results showed that EPIC-BB scores did not change ($0\pm3$) pre- versus post-treatment for the patients who had implanted pre-radiotherapy (n=30) but scores declined by $11\pm14$ for those who did not receive the intervention ($P=0.03$).

2 It is possible that Prada et al (2007) and Prada et al (2009) were contemporary studies with the patients presenting with early stage prostate cancer who were deemed eligible for brachytherapy alone being enrolled in the RCT reported in Prada et al (2009).
Prada et al (2009) reported rectal toxicity. As compared with the control group, patients in the HA group had less mucosal damage post-therapy (5% versus 36%, \( P=0.002 \)) and no macroscopic rectal bleeding (0% versus 12%, \( P=0.047 \)), as assessed using proctoscopic endoscopy.

In follow-up MRIs in the second study by Prada et al (2007), HA injection did not migrate or change in mass or shape by 12 months, and the mean distance between rectum and prostate was 2 cm along the length of the prostate. The median measured rectal radiation dose decreased from 47% to 39% (\( P<0.001 \)).

**COST IMPACT**

No economic studies or cost information were identified in the included literature.

**ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS**

No issues were identified in the included literature.

**OTHER ISSUES**

The only study located for a hydrogel like SpaceOAR was conducted on cadavers (n=20) where hydrogel was injected between the prostate and rectum via a transperitoneal approach (Susil et al 2010). The aim was to quantify the amount of prostate-rectum separation needed for effective rectal dose reduction. Results showed that injection of 20 mL of hydrogel resulted in a mean of 12.5 mm of prostate-rectum separation and simulation studies showed that a prostate-rectum separation of 10 mm was sufficient to reduce the mean rectal volume receiving 70 Gy by 83% (\( P<0.05 \)).

The Cancer Center of Irvine, at which the two most recent studies were conducted, received a $55,000 research grant from Genzyme Corporation to study Hylaform as a tissue spacer in patients undergoing radiotherapy for localised prostate cancer (Wilder et al 2010a & 2010b). Conflict of interest was not reported for Prada et al (2009) and was denied for Prada et al (2007).

**SUMMARY OF FINDINGS**

From the limited literature available (four small studies limited in rigour of design), some form of injected liquid-to-solid inert substance (mostly recently cross-linked hyaluronan gel) for prostate-rectum separation appears to be safe. It also appears to have the potential to lower rates of rectal toxicity and improve QOL for men receiving radiotherapy for prostate cancer. However, the technology is very early in its lifecycle and is not yet in clinical use, although a recent press release notes clinical application of SpaceOAR in Germany. Cost data were not available. Although the treatment paradigm is appealing, more research is definitely needed before conclusions can be reached as to the technology’s potential place in therapy.

**HEALTHPACT ASSESSMENT**

Various inert liquid-to-solid substances for prostate-rectum separation during prostatic radiation therapy (e.g. SpaceOAR) are not yet available in Australia and have also not been specifically approved for this purpose by the US FDA. Although the technology’s potential is appealing, it is still early days. Based on this, it is recommended that the technology be monitored for 24 months.
Inert gels for prostate-rectum separation during prostate radiation therapy

November 2010

**HEALTHPACT ACTION**

**NUMBER OF STUDIES INCLUDED**

- Total number of studies: 4
- Level III-1 evidence: 1
- Level III-3 evidence: 2
- Level IV evidence: 1

**REFERENCES**


**Sources of Further Information**


**Search Criteria to be Used**

SpaceOAR
Hydrogel
Prostate rectum separation
Radiotherapy

**Health PACT Decision**

☐ Horizon Scanning Report  ☐ Full Health Technology Assessment
☐ Monitor  ☐ Archive
☐ Refer  ☐ Decision pending

**Priority Rating**

☐ High  ☐ Medium  ☐ Low