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Department of Health and Ageing



Australia and New Zealand Horizon Scanning Network

ANZHSN

AN INITIATIVE OF THE NATIONAL, STATE AND
TERRITORY GOVERNMENTS OF AUSTRALIA
AND THE GOVERNMENT OF NEW ZEALAND

Horizon scanning technology prioritising summary

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

November 2010



ASERNIP/S

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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)

- | | |
|---|---|
| <input checked="" type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | | |
|---|-------------|----|
| <input type="checkbox"/> Yes | ARTG number | NA |
| <input checked="" type="checkbox"/> No | | |
| <input type="checkbox"/> Not applicable | | |

INTERNATIONAL UTILISATION

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Germany		✓	
United States	✓		
Spain	✓		

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

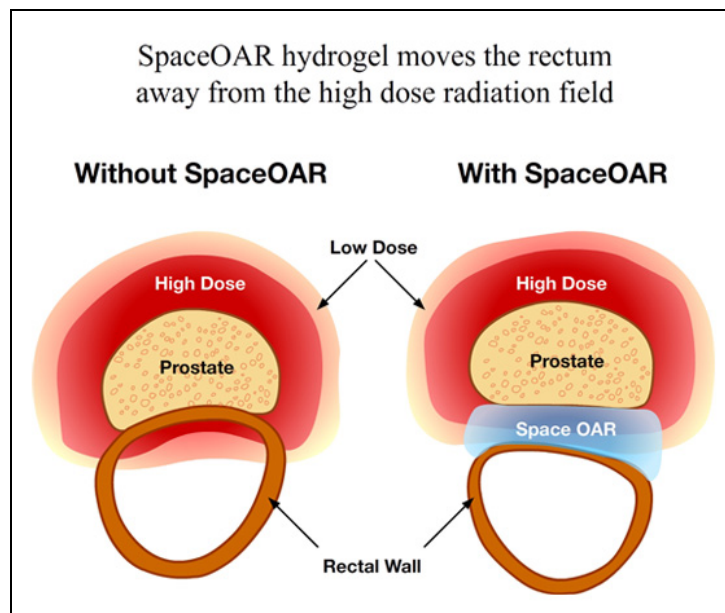
wall by maintaining a space between the prostate and rectum. It then gradually liquefies and is absorbed. Studies located for this summary did not specifically employ SpaceOAR but rather a similar (but naturally-derived) cross-linked hyaluronate gel marketed at that time by Genzyme Inc. (Cambridge, Massachusetts), or other forms of hyaluronic acid used primarily for aesthetic procedures of the face.

BACKGROUND

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/>)



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 Foundation Australia 2010). Prostate cancer is the most common type of cancer in Australian men and is the second most common cause of cancer deaths in males, after lung cancer (Prostate Cancer Foundation Australia 2010; Australian Institute of Health and Welfare 2010). Hospital admissions for a principal diagnosis of prostate cancer almost doubled from 13,715 in 2000-01 to 25,429 in 2005-06 (Australian Institute of Health and Welfare 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

Study, country	Study period	Study group n= Control n=	Study type	Follow-up	Outcome of interest
Wilder et al (2010a), US	09/08 to 03/09	n=10; n=239	Case series w/ historical controls	Median 3 months	Acute rectal toxicity
Wilder et al (2010b), US	06/08 to 06/09	n=30; n=5	Case series w/ contemporary controls	Median 5 months (range 5-12)	Quality of life
Prada et al (2009), Spain	01/05 to 07/06	n=36; n=33	Pseudo-randomised controlled trial	Median 26 months (range 21-39)	Acute rectal toxicity
Prada et al (2007), Spain	Not reported	n=27	Case series	Median 13 months (range 9-22)	Acute rectal toxicity

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) \leq 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

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.

divided among urinary, bowel, sexual and hormonal categories. Within the bowel domain, questions focus on symptom severity and bowel bother (BB).

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 $\geq 3a$ disease with median PSA 21 ng/mL.² 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 ± 13 cGy versus 106 ± 20 cGy in the control group ($P=0.005$).

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).

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 ± 3) pre- versus post-treatment for the patients who had implanted pre-radiotherapy ($n=30$) but scores declined by 11 ± 14 for those who did not receive the intervention ($P=0.03$).

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 ACTION

NUMBER OF STUDIES INCLUDED

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

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SOURCES OF FURTHER INFORMATION

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SEARCH CRITERIA TO BE USED

SpaceOAR
Hydrogel
Prostate rectum separation
Radiotherapy

HEALTH PACT DECISION

- | | |
|--|--|
| <input type="checkbox"/> Horizon Scanning Report | <input type="checkbox"/> Full Health Technology Assessment |
| <input type="checkbox"/> Monitor | <input type="checkbox"/> Archive |
| <input type="checkbox"/> Refer | <input type="checkbox"/> Decision pending |

PRIORITY RATING

- High** **Medium** **Low**