Radiotherapy can be used to treat prostate cancer, but sometimes it can irritate and damage part of the patient's bowel that lies near the prostate. This can cause side effects such as bowel ulceration, bleeding, diarrhoea and incontinence. In this procedure, an absorbable liquid gel is injected, or a balloon is inserted, into the space between the prostate and the rectum, increasing the distance between them. The aim is to reduce the amount of radiation reaching the rectum, so reducing the risk of side effects there.

The National Institute for Health and Care Excellence (NICE) is examining insertion of a biodegradable spacer to reduce rectal toxicity during radiotherapy for prostate cancer and will publish guidance on its safety and efficacy to the NHS. NICE’s interventional procedures advisory committee has considered the available evidence and the views of specialist advisers, who are consultants with knowledge of the procedure. The advisory committee has made draft recommendations about insertion of a biodegradable spacer to reduce rectal toxicity during radiotherapy for prostate cancer.

This document summarises the procedure and sets out the draft recommendations made by the advisory committee. It has been prepared for public consultation. The advisory committee particularly welcomes:

- comments on the draft recommendations
- the identification of factual inaccuracies
- additional relevant evidence, with bibliographic references where possible.

Note that this document is not NICE’s formal guidance on this procedure. The recommendations are provisional and may change after consultation.

The process that NICE will follow after the consultation period ends is as follows.
The advisory committee will meet again to consider the original evidence and its draft recommendations in the light of the comments received during consultation.

The advisory committee will then prepare draft guidance which will be the basis for NICE’s guidance on the use of the procedure in the NHS.

For further details, see the Interventional Procedures Programme process guide, which is available from the NICE website.

Through its guidance NICE is committed to promoting race and disability equality, equality between men and women, and to eliminating all forms of discrimination. One of the ways we do this is by trying to involve as wide a range of people and interest groups as possible in the development of our interventional procedures guidance. In particular, we aim to encourage people and organisations from groups who might not normally comment on our guidance to do so.

In order to help us promote equality through our guidance, we should be grateful if you would consider the following question:

Are there any issues that require special attention in light of NICE’s duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations between people with a characteristic protected by the equalities legislation and others?

Please note that NICE reserves the right to summarise and edit comments received during consultations or not to publish them at all where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would otherwise be inappropriate.

Closing date for comments: 22 July 2016
Target date for publication of guidance: November 2016

1 Draft recommendations

1.1 The evidence on insertion of a biodegradable spacer to reduce rectal toxicity during radiotherapy for prostate cancer raises no major safety concerns. Current evidence on efficacy shows that the insertion of a spacer reduces the dose of radiation to the rectum. However, the evidence that this reduces rectal toxicity and improves patient outcomes in the long term is inadequate.

Therefore, this procedure should only be used with special
arrangements for clinical governance, consent, and audit or research.

1.2 Clinicians wishing to insert a biodegradable spacer to reduce rectal toxicity during radiotherapy for prostate cancer should:

- Inform the clinical governance leads in their NHS trusts.
- Ensure that patients understand the uncertainty about the procedure’s safety and efficacy, and provide them with clear written information. In addition, the use of NICE’s information for the public is recommended.
- Audit and review clinical outcomes of all patients having insertion of a biodegradable spacer to reduce rectal toxicity during radiotherapy for prostate cancer (see section 7.1).

1.3 The procedure should only be done by clinicians with training in and experience of transperineal interventional procedures.

1.4 NICE encourages further research into the insertion of biodegradable spacers to reduce rectal toxicity during radiotherapy for prostate cancer. Studies should clearly describe the type of spacer and radiotherapy used, patient selection and indications. Outcome measures should include radiation proctitis, disease progression, long-term survival and patient reported outcomes in the short and long term.

1.5 NICE may update the guidance on publication of further evidence.

2 **Indications and current treatments**

2.1 Current treatment options for localised or locally advanced prostate cancer include 'watchful waiting', active surveillance, radiotherapy, radical prostatectomy, transurethral resection of the prostate,
cryotherapy, high-intensity focused ultrasound, androgen deprivation therapy and chemotherapy (as recommended in NICE’s guideline on prostate cancer: diagnosis and treatment).

2.2 Radiation therapy is an established curative treatment and can either be external-beam radiotherapy or brachytherapy (also called interstitial radiotherapy). Brachytherapy can be given at either low- or high-dose rates. Low-dose rate brachytherapy may be used alone (monotherapy) or in combination with external-beam radiotherapy.

3 The procedure

3.1 Radiotherapy for prostate cancer can cause rectal damage because of the close proximity of the prostate and the rectum. Symptoms include diarrhoea, incontinence, proctitis and ulceration of the rectal mucosa. The aim of injecting a biodegradable substance (examples include polyethylene glycol hydrogel, hyaluronic acid, and human collagen), or inserting and inflating a biodegradable balloon spacer, in the space between the rectum and prostate is to temporarily increase the distance between them. The aim is to reduce the amount of radiation delivered to the rectum, and reduce the toxicity to the rectum during prostate radiotherapy.

3.2 The procedure is usually done with the patient under general anaesthesia. However, it may be done using local or spinal anaesthesia, depending on the 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...
hydrodissection with saline. Once the correct positioning of the needle is confirmed, the biodegradable spacer substance is injected as liquid into the perirectal space. It then polymerises with the saline to form a soft absorbable mass. The spacer degrades slowly over several months. With balloon spacer insertion, a small perineal incision is typically used to insert a dilator and introducer sheath. Using ultrasound guidance, the dilator is advanced towards the prostate base over the needle, which is then removed. A biodegradable balloon is introduced through the introducer sheath and is filled with saline and sealed with a biodegradable plug. The balloon spacer degrades over several months.

4 Efficacy

This section describes efficacy outcomes from the published literature that the committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the interventional procedure overview.

Spacers with external beam radiation therapy

4.1 In a prospective multicentre randomised controlled trial (RCT) of 222 patients with prostate cancer comparing hydrogel spacer injection (hydrogel, n=148) with no spacer injection as control (n=72) during image-guided intensity-modulated radiation therapy (IG-IMRT), spacer placement success (defined as hydrogel present in the perirectal space) was reported in 99% (146/148) of patients in the spacer group. In a case series of 27 patients with a biodegradable balloon inserted for prostate rectum separation during radiotherapy, balloon placement success was reported in 96% (26/27) of patients.
4.2 In the prospective multicentre RCT of 222 patients, perirectal space (defined as the distance between the posterior prostate capsule and anterior rectal wall on axial mid-gland T2-weighted MRIs) after hydrogel insertion was 1.26±0.39 cm in the spacer group and 0.16±0.20 cm in the control group respectively (no statistical significance reported). In the case series of 27 patients, the distance between the prostate and rectum increased 10-fold from a mean of 0.22±0.20 cm to 2.47±0.47 cm after balloon insertion. The distance remained constant throughout radiotherapy (2.47±0.47 cm and 2.41±0.43 cm respectively.

4.3 In the prospective multicentre RCT of 222 patients, acute rectal toxicity was similar between the spacer and control groups (p=0.525), as was urinary tract toxicity (p=0.488). There was statistically significantly less rectal toxicity at 3–15 months in patients with a spacer (2% of patients: rectal bleeding, rectal urgency and proctitis, each in 1 patient) compared with patients in the control group (7% of patients: rectal bleeding in 3, rectal urgency in 1 and grade 3 proctitis in 1; p=0.04). There was no late rectal toxicity greater than grade 1 (assessed using the National Cancer Institute’s Common Terminology Criteria for Adverse Events grading system) in patients in the spacer group. In a comparative case series of 78 patients comparing hydrogel spacer (n=30) with biodegradable balloon spacer (n=29) and no spacer (n=19), there were no statistically significant differences in acute toxicity between spacer and control groups 3 months after radiotherapy for any genitourinary, gastrointestinal or combined grade 2 toxicities.

4.4 In the prospective multicentre RCT of 222 patients, there was a statistically significant reduction in mean rectal dose volume within
the 70 Gy isodose in patients in the spacer group (from baseline, 12.4% to 3.3% after spacer injection, p<0.001) compared with patients in the control group (from baseline, 12.4% to 11.7%). In the comparative case series of 78 patients, there was a statistically significant reduction in rectal dose in the balloon spacer group (by 27.7%, p=0.034). However, there was an average volume loss of more than 50% during the full course of treatment of 37-40 fractions; the volume of hydrogel spacers remained fairly constant.

4.5 In the prospective multicentre RCT of 222 patients, at 15-month follow-up, 12% of patients in the spacer group and 21% of patients in the control group reported a 10-point similar decline (p=0.087) in bowel quality-of-life scores (assessed using the Expanded Prostate Cancer Index Composite self-assessment questionnaire). At 6-month follow-up, 9% of patients in the spacer group and 22% of patients in the control group reported a 10-point decline in urinary scores (p=0.003). At 12- and 15-month follow-up, the declines in urinary quality-of-life scores were similar for both groups.

4.6 In the prospective multicentre RCT of 222 patients, hydrogel absorption was confirmed at 12 months (on MRI scans) in all the patients in the spacer group and only 2% (3/148) of them had small water density remnant cysts in perirectal tissues. In the case series of 27 patients, 17% (4/23) of balloons deflated prematurely at 3-month follow-up. This was presumed to be secondary to previously implanted fiducial markers. At 6-month follow-up, the balloons had deflated and been absorbed in all except 2 patients. In the comparative case series of 78 patients, at 6-month follow-up, hydrogel spacers were completely absorbed in all patients. In the balloon group, empty balloon envelopes were visible in 28%
patients but showed no volume effect, and surrounding tissue was unaltered with no signs of fibrosis or inflammation.

4.7 The specialist advisers listed key efficacy outcomes as reduction of radiation dose to the rectum during radiotherapy, reduction in rectal toxicity, and increase in space and distance between the prostate and rectum.

5 Safety

This section describes safety outcomes from the published literature that the committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the interventional procedure overview.

5.1 One case of intravascular injection of hydrogel spacer was reported on the US Food and Drug Administration Manufacturer and User Facility Device Experience database. The clinician stated that, on T2-weighted MRI, the gel was seen casting out a vein, starting at the perirectal space and coursing up to the common iliac vein. Proximally, the hydrogel appeared to cast out the entire vessel, while distally a smaller strand of gel was seen within the artery. The clinician stated that this might have been caused by needle tip movement into the vein after aspiration and before hydrogel injection, allowing the hydrogel to enter the vessel. The patient remained asymptomatic and was prescribed a low-dose anticoagulant daily as prophylaxis against venous thrombosis. Radiation treatment was given as planned.

5.2 Inadvertent rectal wall injection (with hydrogel) resulting in focal rectal mucosal necrosis and bladder perforation was reported after
the procedure in 1 patient in a case series of 52 patients. This resolved with no sequelae.

5.3 A rectal ulcer, 1 cm in diameter and causing frequent rectal bleeding, mucus discharge and bowel movements, was reported in a case report of 1 patient 2 months after hydrogel injection. This had resolved without further intervention by 3 months. Digital rectal examination at 6 months revealed a healed ulcer, with only a non-tender slit in the anterior rectal wall. At subsequent examinations over 3 years, there was no recurrence of bowel symptoms.

5.4 Haematoma developed behind the bladder in 1 patient with a moderate platelet count (within hours after injection) in a case series of 36 patients injected with a hyaluronic acid spacer. This was removed by laparotomy.

5.5 Infections (bacterial peritonitis in 2 patients and bacterial epididymitis in 1 patient) were reported in 3% (3/100) of patients injected with a hydrogel spacer in a retrospective comparative case series of 200 patients. The bacterial peritonitis occurred after prostate biopsies. All 3 infections resolved with antibiotic therapy. No infections were reported in the 100 patients treated with high dose rate brachytherapy without hydrogel.

5.6 Penile bleeding was reported in 1 patient during balloon insertion in a case series of 27 patients. Further details were not reported.

5.7 Acute urinary retention (needed catheterisation, which resolved within a few hours) was reported in 12% (3/26) of patients during balloon insertion and in 1 patient during radiotherapy in the case series of 27 patients.
5.8 Dysuria and nocturia (grade 1–2) was reported in 12% (3/26) of patients during balloon insertion and in 65% (15/23) of patients during radiotherapy in the case series of 27 patients. Further details were not reported. Other events reported during radiotherapy in the same study included diarrhoea in 17% (4/23) of patients, mild proctitis in 8% (2/23) of patients and, in 1 patient each, blood in the faeces, constipation, erectile dysfunction, itching, fatigue and decreased urine flow.

5.9 Acute rectal pain was statistically significantly reduced in patients in the spacer group compared with those in the control group in a randomised controlled trial of 222 patients (spacer: 3%, control 11%; p=0.02).

5.10 In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never done so). For this procedure, specialist advisers listed no anecdotal adverse events. They considered that the following were theoretical adverse events: damage to urethra, and prostate; allergy; and unknown long-term effects of the hydrogel spacer.

6 Committee comments

6.1 The committee noted that a variety of materials have been used as biodegradable spacers. Some were not CE marked for this indication and so have not been considered. Most of the evidence seen by the committee was on the use of hydrogel, with less evidence on the use of other materials.
6.2 The committee noted that spacers have been used with both external beam radiotherapy and brachytherapy.

7 Further information

7.1 This guidance requires that clinicians doing the procedure make special arrangements for audit. NICE has identified relevant audit criteria and is developing an audit tool (which is for use at local discretion). This tool will be available when the guidance is published.

7.2 For related NICE guidance, see the NICE website.

Tom Clutton-Brock
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June 2016