

Biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer

Interventional procedures guidance

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Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

1 Recommendations

- 1.1 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.
- 1.2 The procedure should only be done by clinicians with training in, and experience of, transperineal interventional procedures.

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, 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 be either 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 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 to the rectum. Symptoms include diarrhoea, incontinence, proctitis and ulceration of the rectal mucosa. 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 done 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 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 a 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](#).

Only evidence on CE-marked spacers has been considered and these have only been used with studies of 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 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).

- 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 to 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; $p=0.04$). The 3-year incidence of rectal toxicity higher than grade 1 (2.0% compared with 9.2%; $p=0.028$) and higher than grade 2 (0% compared with 5.7%; $p=0.012$) was statistically significantly lower in the spacer group than control group. Urinary toxicity of higher than grade 1 was also lower in the spacer arm (4% compared with 15%; $p=0.046$), with no difference in higher than grade 2 urinary toxicity between the groups (7% compared with 7%; $p=0.7$). 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 to 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 decline ($p=0.087$) in bowel quality-of-life scores (assessed using the Expanded Prostate Cancer Index Composite self-assessment questionnaire). Bowel quality of life consistently favoured the spacer group from 6 months ($p=0.002$), with a 5.8-point difference at 3 years ($p<0.05$)

meeting the threshold for a minimally important difference (MID, 5 points). At 3 years, more men in the control group than in the spacer group had experienced a MID decline in bowel quality of life (5-point decline: 41% compared with 14%; $p=0.002$; odds ratio [OR] 0.28, 95% confidence interval [CI] 0.13 to 0.63). At 3-year follow-up, the control group had a 3.9-point greater decline in urinary quality of life compared with the spacer group ($p<0.05$), but the difference did not meet the MID threshold (6 points). At 3 years, more men in the control group than in the spacer group had experienced a MID decline in urinary quality of life (6-point decline: 30% compared with 17%; $p=0.04$; OR 0.41, 95% CI 0.18 to 0.95) and even large declines at twice the MID (12-point decline: 23% compared with 8%; $p=0.02$; OR 0.31, 95% CI 0.11 to 0.85).

- 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, with 2% (3/148) of them having 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.
- 4.8 One commentary from a patient who had experience of this procedure was received, which was discussed by the committee.

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 (FDA) Manufacturer and User Facility Device Experience (MAUDE) database. The clinician stated that this might have been caused by needle tip movement into a 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 (which needed catheterisation, and 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 to 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 As well as 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.
- 5.10 One commentary from a patient who had experience of this procedure was received, which was discussed by the committee.

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 evidence on efficacy from studies of these spacers was not considered. Most of the evidence on CE-marked spacers 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 For related NICE guidance, see the [NICE website](#).

Information for patients

NICE has produced information on this procedure for patients and carers ([information for the public](#)). It explains the nature of the procedure and the guidance issued by NICE, and has been

written with patient consent in mind.

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Endorsing organisation

This guidance has been endorsed by [Healthcare Improvement Scotland](#).

Accreditation

