

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional procedure consultation document

Preoperative high dose rate brachytherapy for rectal cancer

Rectal cancer is a common form of bowel cancer that affects the rectum (end part end of the bowel). In preoperative high dose rate brachytherapy radioactive material is put within, or close to, the cancer to shrink it before surgery.

The National Institute for Health and Care Excellence (NICE) is examining preoperative high dose rate brachytherapy for rectal 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 provisional recommendations about preoperative high dose rate brachytherapy for rectal cancer.

This document summarises the procedure and sets out the provisional recommendations made by the Advisory Committee. It has been prepared for public consultation. The Advisory Committee particularly welcomes:

- comments on the provisional 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 provisional 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- The Advisory Committee will then prepare draft guidance which will be the basis for NICE's guidance on the use of the procedure in the NHS.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: 21 April 2015

Target date for publication of guidance: 22 July 2015

1 Provisional recommendations

- 1.1 Current evidence on the safety of preoperative high dose rate brachytherapy for rectal cancer and its efficacy in reducing tumour size appears adequate. However, there is no evidence that the procedure provides additional benefit when used as a boost to external beam radiotherapy. Evidence on the efficacy of the procedure if used without external beam radiotherapy is inadequate in quantity. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

- 1.2 Clinicians wishing to undertake preoperative high dose rate brachytherapy for rectal cancer should take the following actions:
- Inform the clinical governance leads in their NHS trusts.
 - Ensure that patients understand the uncertainty about the procedure's 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 preoperative high dose rate brachytherapy for rectal cancer (see section 6.2).
- 1.3 Patient selection should be done by a colorectal cancer multidisciplinary team which includes a clinical oncologist and a colorectal surgeon with expertise in local excision techniques.
- 1.4 NICE encourages further research into preoperative high dose rate brachytherapy for rectal cancer. Trials should be designed to provide clear data on the efficacy of this procedure, whether or not other adjunctive treatments are used. Research should document adjunctive treatments and details of patient selection. Outcomes should include local recurrence, survival, disease-free survival and quality of life. NICE may update the guidance on publication of further evidence.

2 Indications and current treatments

- 2.1 Rectal cancer is a common form of bowel cancer. The likelihood of developing it rises sharply with age. Symptoms include rectal bleeding and change in bowel habit, although the early stages may be asymptomatic.

- 2.2 Surgery is the main treatment for patients with rectal cancer who are treated with curative intent. It involves resection of the affected part of the rectum and the mesorectum. The anal sphincter is preserved whenever possible: a colostomy is formed when this is not possible.
- 2.3 In some patients, radiotherapy or chemotherapy or both are used before, during or after surgery to decrease the chances of local recurrence and metastatic disease. Radiotherapy may take the form of external beam radiation therapy (EBRT) or brachytherapy. EBRT uses radiation from outside the body, which is focussed on the cancer and surrounding lymph nodes. Brachytherapy involves placing a radioactive source (pellet, seed or catheter) directly into or near the tumour. In contact brachytherapy (the Papillon technique) a low energy X-ray tube is used to deliver radiation to the tumour with limited penetration.
- 2.4 Preoperative high dose rate endorectal brachytherapy uses localised radiotherapy, with the aim of shrinking the tumour before surgery with fewer side effects than EBRT.

3 The procedure

- 3.1 Endorectal high dose rate (HDR) brachytherapy for rectal cancer is usually carried out with the patient under sedation. Before treatment the tumour size and stage are determined using imaging techniques. A 3-dimensional CT-based treatment planning system may be used to guide the positioning and dose of radiation. Radio-opaque clips may be placed, using proctoscopy or sigmoidoscopy, to mark the margins of the tumour.

- 3.2 A rigid or flexible endorectal applicator is inserted into the rectum and used to deliver the radiation source to the tumour. The radioactive material is moved from the brachytherapy machine into the applicator and is left in place to deliver the correct dose of radiation to the tumour. A balloon may be placed over the applicator to displace the uninvolved rectal mucosa away from the radioactive material, to reduce toxicity. When the balloon is inflated, it immobilises the applicator and also helps to facilitate close contact with the tumour. When the treatment is over, the radioactive material is moved back into the machine and the applicator is taken out. Surgery to remove any remaining tumour is done a few weeks after completion of brachytherapy

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](#).

- 4.1 A randomised controlled trial (RCT) of 221 patients treated by a preoperative high dose rate (HDR) brachytherapy boost and external beam radiotherapy (EBRT) or by EBRT alone, with concomitant chemotherapy, reported that 66% of 2-year survivors and 65% of 5-year survivors had a stoma, with no difference between the groups ($p=1.00$). A non-randomised comparative study of 230 patients treated by preoperative brachytherapy or by surgery alone reported that the sphincter was preserved in 72% (69/96) of patients treated by preoperative brachytherapy compared against 42% (48/115) of patients treated by surgery alone ($p<0.0001$).

- 4.2 An RCT of 243 patients treated by a preoperative HDR brachytherapy boost and EBRT or by EBRT alone, with concomitant chemotherapy, reported R0 resection (complete resection with no microscopic residual tumour) in 99% (87/90) and 90% (83/92) of patients, respectively ($p=0.03$). A non-randomised comparative study of 954 patients treated by preoperative HDR brachytherapy, by short course EBRT or by surgery alone reported R0 resection in 97% (307/318), 83% (265/318) and 74% (236/318) of patients, respectively ($p=0.5$ for preoperative brachytherapy versus short course EBRT).
- 4.3 The RCT of 243 patients treated by a preoperative HDR brachytherapy boost and EBRT or by EBRT alone, with concomitant chemotherapy, reported a 'major response' in 44% (35/80) and 28% (23/82) of patients, respectively ($p=0.04$). The difference in response rate was greater for tumours less than 3.7 cm in diameter. A case series of 285 patients reported a complete pathological response rate of 27% after preoperative HDR brachytherapy and surgery.
- 4.4 The non-randomised comparative study of 230 patients reported that 8% (8/96) of patients treated by preoperative brachytherapy developed local recurrence, compared against 21% (24/115) of patients treated by surgery alone ($p=0.005$). The case series of 285 patients reported an actuarial local recurrence rate of 5% at 5 years after preoperative HDR brachytherapy and surgery.
- 4.5 The RCT of 221 patients treated by a preoperative HDR brachytherapy boost and EBRT or by EBRT alone, with concomitant chemotherapy, reported progression-free 5-year survival of 52% and 64%, respectively ($p=0.32$). The non-

randomised comparative study of 230 patients reported disease-free survival of 72% (69/96) for patients treated by preoperative brachytherapy (median follow-up 49.5 months) compared against 65% (75/115) for patients treated by surgery alone (median follow-up 47.5 months; p value not stated). The case series of 285 patients reported 5-year disease-free survival of 65% after preoperative HDR brachytherapy and surgery.

- 4.6 The RCT of 221 patients treated by a preoperative HDR brachytherapy boost and EBRT or by EBRT alone, with concomitant chemotherapy, reported overall 5-year survival of 64% and 71%, respectively ($p=0.34$). The non-randomised comparative study of 230 patients reported actuarial probability of 5-year survival of 62% for patients treated by preoperative brachytherapy and 65% for patients treated by surgery alone. The case series of 285 patients reported 5-year overall survival of 68% after preoperative HDR brachytherapy and surgery.
- 4.7 The specialist advisers listed the following key efficacy outcomes: sphincter preservation rate compared with conventional therapy; histopathological outcomes of surgery; R0 resection rates; quality of life; bowel, urinary and sexual function; local recurrence rates; disease-free survival and overall survival.

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 The following grade 2 toxicity events were reported in patients treated by a preoperative high dose rate (HDR) brachytherapy boost and external beam radiotherapy (EBRT) with concomitant chemotherapy in a randomised controlled trial (RCT) of 243 patients: 'skin' (20%), diarrhoea (19%), proctitis (18%), nausea (6%), dysuria (6%), vomiting (2%), stomatitis (2%), and neutropaenia (1%). Similar rates were seen in patients treated by preoperative EBRT alone with concomitant chemotherapy. Grade 3 acute proctitis was reported in 1% (2/285) of patients in a case series of 285 patients treated by preoperative HDR brachytherapy. Rectal pain was reported in 71% (12/17) of patients treated by preoperative HDR brachytherapy in a non-randomised comparative study of 36 patients.

5.2 Wound infection was reported in 15% (16/106) of patients treated by a preoperative HDR brachytherapy boost and EBRT compared against 11% (12/109) of patients treated by preoperative EBRT alone in the RCT of 243 patients. 'Infection' was reported in 9% (30/318), 8% (26/318) and 6% (20/318) of patients treated by preoperative HDR brachytherapy, by EBRT or by surgery alone, respectively, in the non-randomised comparative study of 954 patients ($p=0.2$). In the same study wound infection was reported in 9% (29/318), 12% (39/318) and 6% (19/318) of patients treated by preoperative HDR brachytherapy, by EBRT or by surgery alone, respectively ($p=0.25$), and intra-abdominal infection was reported in 4% (12/318), 3% (8/318) and 3% (9/318) of patients, respectively ($p=0.4$). Pelvic sepsis and wound sepsis were each reported in 4% (4/106) of patients in a case series of 106 patients.

- 5.3 Wound dehiscence was reported in 3% (9/318), 3% (8/318) and 2% (5/318) of patients treated by preoperative HDR brachytherapy, by EBRT or by surgery alone, respectively, in the non-randomised comparative study of 954 patients ($p=0.4$). Anastomotic dehiscence was reported in 4% (13/318), 6% (20/318) and 4% (13/318) of patients treated by preoperative HDR brachytherapy, by EBRT or by surgery alone, respectively, in the non-randomised comparative study ($p=0.2$) and in 4% (4/106) of patients in the case series of 106 patients.
- 5.4 Fistula was reported in less than 1% (1/106) of patients treated by a preoperative HDR brachytherapy boost and EBRT, and in 2% (2/109) of patients treated by preoperative EBRT alone, in the RCT of 243 patients. Fistula was reported in 7% (7/106) of patients in the case series of 106 patients.
- 5.5 'Stricture' was reported in 1 patient in a case series of 34 patients. Anastomotic stricture was reported in 3% (3/106) of patients in the case series of 106 patients.
- 5.6 Small bowel obstruction was reported in 8% (8/106) of patients in the case series of 106 patients; all were successfully treated without surgery.
- 5.7 Reoperation was reported in 5% (5/106) of patients treated by a preoperative HDR brachytherapy boost and EBRT compared against 8% (9/109) of patients treated by EBRT alone, in the RCT of 243 patients (p value not reported). Reoperation rates of 4% (13/318), 14% (45/318) and 12% (39/318) were reported for patients treated by preoperative HDR brachytherapy, by short course EBRT or by surgery alone, respectively ($p=0.0005$), in the non-randomised comparative study of 954 patients. Surgical
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intervention for complications was reported in 11% (12/106) of patients in the case series of 106 patients.

- 5.8 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 the following anecdotal adverse events: rectal fistula formation, small bowel stricture, and persisting proctitis. They considered that the following were theoretical adverse events: bladder perforation, mucosal damage causing ulceration and bleeding, stenosis of the rectal lumen or small bowel, and skin changes on the perineum.

6 Further information

- 6.1 For related NICE guidance, see the [NICE website](#).
- 6.2 This guidance requires that clinicians undertaking 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), which will be available when the guidance is published.
- 6.3 This guidance is a review of 'Preoperative high dose rate brachytherapy for rectal cancer' NICE interventional procedure guidance 201 (2006).

Bruce Campbell

Chairman, Interventional Procedures Advisory Committee

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