

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of preoperative high dose rate brachytherapy for rectal cancer

Rectal cancer is a common form of bowel cancer. Preoperative high dose rate brachytherapy involves placing radioactive material in or close to the cancer to shrink the tumour before surgery.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in May 2006

Procedure name

- Endorectal high dose rate (HDR) brachytherapy
- HDR afterloading brachytherapy
- Endocavitary HDR brachytherapy
- Intraluminal HDR brachytherapy

Specialty societies

- Association of Coloproctology of Great Britain and Ireland
- Royal College of Radiologists

Description

Indications

Cancer in the middle or lower third of the rectum.

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The probability of developing rectal cancer rises sharply with age. Symptoms include rectal bleeding and change in bowel habit, although the early stages may be asymptomatic.

In addition to the universal TNM cancer staging system, rectal cancers are conventionally staged using Dukes' classification system. In Dukes' system, stage A means the tumour is confined to the lining of the rectum, stage B means the tumour has grown into the muscle wall, stage C means the cancer has spread to at least one lymph node in the area, and stage D refers to cancer that has spread to another organ in the body.

Current treatment and alternatives

Among patients who can be treated with a curative intent, surgery is the main treatment modality. It involves resection of the affected part of the rectum, with or without preservation of the anus (and formation of a colostomy when preservation of the anus is not technically possible). In some patients, radiotherapy and chemotherapy may also be used before, during or after surgery in an attempt to decrease local recurrence and prevent metastatic disease.

Three main types of radiotherapy can be used to treat rectal cancer. The most common are external beam radiation therapy (EBRT) and brachytherapy. EBRT uses radiation from outside the body to focus on the cancer and surrounding lymph nodes. Brachytherapy involves the placement of a radioactive source (pellet, seed or catheter) directly into or near the tumour. Less commonly, contact radiotherapy with a contact x-ray tube that delivers radiation with limited penetration (Papillon technique) has also been used to treat early rectal cancer.

What the procedure involves

Endorectal HDR brachytherapy for rectal cancer is usually carried out under sedation. Before treatment the tumour size and stage is determined using imaging techniques, and a three-dimensional computed tomography (CT)-based treatment planning system may be used to determine source positioning and appropriate dosing. Radio-opaque clips may also be placed to mark the margins of the tumour, using proctoscopy or sigmoidoscopy. An endorectal applicator is used to deliver radiation to the tumour within the rectum; the applicator may be rigid or it may have a balloon-type device within it, which is inflated to immobilise the applicator and to facilitate close contact with the tumour. Catheters within the applicator are subsequently loaded (this is at times termed 'afterloading') with the radioactive source, according to the treatment plan.

Brachytherapy can be administered at low or high dose rates. In principle the higher the dose rate the greater the amount of radiation that is delivered over a shorter time interval – this means that the total radiation dose may in fact be lower with some high dose rate regimens than low dose rate treatments.

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HDR brachytherapy may be used preoperatively on its own or as a boost after EBRT. The aim of preoperative brachytherapy is to help shrink (down-stage) the cancer, which may make anal preservation surgery more feasible for some patients. Once the treatment is completed, the patient is scheduled for surgery to remove any remaining tumour, usually within a few weeks of the brachytherapy treatment.

Efficacy

The efficacy evidence presented in this overview relates to one non-randomised controlled trial and one case series.^{1,3,4}

The Specialist Advisors listed key efficacy outcomes as sphincter preservation, quality of life (including long-term bowel function), local recurrence rates, disease-free survival and overall survival.

Sphincter preservation surgery

A non-randomised comparative study reported that 72% (69/96) of patients treated with intraluminal brachytherapy had sphincter preserving resection, compared with 42% (48/115) of controls treated with surgery alone ($p < 0.0001$).¹

A case series of 49 patients reported that a complete clinical response (no tumour defined as no macroscopic disease seen at the time of surgery) was achieved for 64% (30/47) patients.^{3,4}

Local recurrence

The non-randomised comparative study reported that 8% (8/96) of patients treated with intraluminal brachytherapy developed local recurrence, compared with 21% (24/115) of patients treated with surgery alone ($p = 0.005$).¹

Disease-free survival

The non-randomised comparative study reported disease-free survival at follow-up for 72% (69/96) patients treated with brachytherapy (median follow-up 49.5 months) compared with 65% (75/115) for controls treated with surgery alone (median follow-up 47.5 months) (p value not stated).¹

Overall survival

The non-randomised comparative study reported actuarial probability of 5-year survival of 62% for patients treated with brachytherapy and 65% for controls treated with surgery alone.¹

Safety

The safety evidence presented in this overview relates to one non-randomised controlled trial and three case series studies.¹⁻⁶

The Specialist Advisors stated that potential adverse effects of the procedure include rectal or bladder perforation, mucosal damage causing ulceration and bleeding, stenosis of the rectal lumen, fistula formation between the rectum and the bladder or the vagina, myocardial infarction and stroke.

Acute toxicity

The non-randomised comparative study reported that 74% (14/19) of patients treated with a high total dose and 38% (36/96) of patients treated with a moderate total dose had brachytherapy-related complications such as radiation ileitis and perianal skin problems.¹ A case series including 49 patients reported that 100% (49/49) of patients developed proctitis and 4% (2/49) developed dermatitis.^{3,4}

Small bowel perforation

One case series reported small bowel perforation in 0% (0/87) of patients treated with a moderate dose and 11% (2/19) of patients treated with a high dose.²⁻⁴

Fistula formation

Two case series reported fistula formation in 5% (4/87) of patients treated with a moderate dose and 16% (3/19) of patients treated with a high dose. A second case series reported fistula formation in 15% (6/41) of patients.^{2,5}

Wound or anastomotic dehiscence

One case series reported perineal dehiscence in 24% (10/41) of patients after abdominoperineal resection.⁵ Another case series reported anastomotic dehiscence in 5% (4/87) of patients treated with a moderate dose and wound sepsis in 5% (1/19) of patients treated with a high dose and 3% (3/87) of patients treated with a moderate dose of brachytherapy.² A third case series reported wound infection in 6% (3/48) of patients receiving surgery after chemoradiotherapy and a brachytherapy boost.⁶

Small-bowel obstruction

One case series reported small-bowel obstruction in 11% (2/19) of patients in the high dose group and 7% (6/87) of patients in the moderate dose group, all successfully treated without surgery.² A second case series reported that 10% (4/41) of patients had small-bowel obstruction, three of whom required surgical intervention.⁵

Anastomotic stenosis

Anastomotic stenosis or stricture was reported in 3% (3/87) and 4% (2/49) of patients.²⁻⁴

Pelvic sepsis

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One case series reported pelvic sepsis in 11% (2/19) of patients in the high dose group and 2% (2/87) of patients in the moderate dose group. Another case series reported that 6% (3/49) of patients developed a pelvic abscess.²⁻⁴

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to high dose rate brachytherapy for rectal cancer. Searches were conducted via the following databases, covering the period from their commencement to 15 February 2006: Medline, PreMedline, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches. (See appendix C for details of search strategy.)

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with rectal cancer suitable for resection.
Intervention/test	Preoperative high dose rate brachytherapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on one non-randomised comparative study¹ and five case series.²⁻⁶ One of the case series included patients from the same study centre as the non-randomised comparative study.² Two case series described different aspects of the same study.^{3,4}

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Existing reviews on this procedure

There were no published systematic reviews identified at the time of the literature search.

Related NICE Guidance

Below is a list of NICE guidance related to this procedure. Appendix B details the recommendations made in each piece of guidance listed below.

Cancer Service Guidance

- Improving outcomes in colorectal cancers: Manual update (June 2004)

Table 2 Summary of key efficacy and safety findings on preoperative high dose rate brachytherapy for rectal cancer

Abbreviations used: EBRT, external beam radiation therapy; HDR, high dose rate; IBT, intraluminal brachytherapy therapy; MRI, magnetic resonance imaging																							
Study details	Key efficacy findings	Key safety findings	Comments																				
<p>Yanagi H (1997)¹</p> <p>Non-randomised controlled study (retrospective)</p> <p>Japan</p> <p>Study period: October 1986–October 1995</p> <p>n = 230</p> <p>Population: Patients with rectal cancer in the middle or lower rectum</p> <ul style="list-style-type: none"> 42% (96/230) preoperative IBT (moderate dose) and radical surgery 8% (19/230) preoperative IBT (high dose) and radical surgery 50% (115/230) surgery alone <p>Median age (years):</p> <ul style="list-style-type: none"> Moderate dose IBT = 59 (range 25–87) High dose IBT = 65 (range 46–86) Control group = 59 (range 30–83) <table border="1"> <thead> <tr> <th>Dukes' stage</th> <th>IBT group (moderate dose)</th> <th>IBT group (high dose)</th> <th>Control group</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>33% (32/96)</td> <td>37% (7/19)</td> <td>27% (31/115)</td> </tr> <tr> <td>B</td> <td>17% (16/96)</td> <td>16% (3/19)</td> <td>28% (32/115)*</td> </tr> <tr> <td>C</td> <td>43% (41/96)</td> <td>26% (5/19)</td> <td>38% (44/115)</td> </tr> <tr> <td>D</td> <td>7% (7/96)</td> <td>21% (4/19)</td> <td>7% (8/115)</td> </tr> </tbody> </table> <p>* p = 0.009</p>	Dukes' stage	IBT group (moderate dose)	IBT group (high dose)	Control group	A	33% (32/96)	37% (7/19)	27% (31/115)	B	17% (16/96)	16% (3/19)	28% (32/115)*	C	43% (41/96)	26% (5/19)	38% (44/115)	D	7% (7/96)	21% (4/19)	7% (8/115)	<p>Sphincter-saving resection</p> <ul style="list-style-type: none"> High dose IBT = 63% (12/19) Moderate dose IBT = 72% (69/96) Controls = 42% (48/115) <p>p < 0.0001 (moderate dose versus controls)</p> <p>Lymph node metastases localised in perirectal tissue (Dukes' C patients)</p> <ul style="list-style-type: none"> High dose IBT = 40% (2/5) Moderate dose IBT = 73% (30/41) <p>Controls = 34% (15/44)</p> <p>p = 0.02</p> <p>Local recurrence</p> <ul style="list-style-type: none"> High dose IBT = 5% (1/19) Moderate dose IBT = 8% (8/96) Controls = 21% (24/115) <p>p = 0.005</p> <p>Distant recurrence</p> <ul style="list-style-type: none"> High dose IBT = 16% (3/19) Moderate dose IBT = 23% (22/96) Controls = 17% (19/115) <p>Disease-free survival</p> <ul style="list-style-type: none"> High dose IBT = 68% (13/19) Moderate dose IBT = 72% (69/96) Controls = 65% (75/115) <p>Actuarial probability of local recurrence at 5 years (Kaplan–Meier)</p> <ul style="list-style-type: none"> High dose IBT (actual recurrence) = 6% Moderate dose IBT = 11% Controls = 26% 	<p>IBT-related complications (such as radiation ileitis and proctitis)</p> <ul style="list-style-type: none"> High dose IBT = 74% (14/19) Moderate dose IBT = 38% (36/96) <p>Surgical interventions for complications were required in 37% (7/19) patients in high dose group and 7% (7/96) patients in moderate dose group.</p> <p>16% (3/19) patients in high dose group were converted to permanent stoma after initial sphincter sparing resection because of complications.</p> <p>The paper reports that after coloanal anastomosis many patients in the high dose IBT group had diarrhoea and faecal incontinence in the early postoperative period and urgency and incomplete evacuation later on.</p>	<p>63 control patients underwent surgery between 1978 and 1986 before IBT was introduced. The remaining 52 control patients were recruited at a period that IBT was available but chose not to be treated with it.</p> <p>There were statistically significant differences in the preoperative tumour stage between treated cases and controls in terms of Dukes' classification and histological differentiation.</p> <p>Moderate dose IBT was defined as 16–40 Gy and high dose as 40–80 Gy.</p> <p>'Moderate' and 'high' dose relates to the total dose of radiation rather than the dose rate.</p> <p>Although the paper does not state that this is high dose rate brachytherapy, it is cited as being so by Vuong et al.</p>
Dukes' stage	IBT group (moderate dose)	IBT group (high dose)	Control group																				
A	33% (32/96)	37% (7/19)	27% (31/115)																				
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Abbreviations used: EBRT, external beam radiation therapy; HDR, high dose rate; IBT, intraluminal brachytherapy therapy; MRI, magnetic resonance imaging																												
Study details				Key efficacy findings		Key safety findings		Comments																				
Yanagi H (1997) <i>contd</i>				Actuarial probability of survival rate for 5 years (Kaplan–Meier) <ul style="list-style-type: none"> • High dose IBT = 63% • Moderate dose IBT = 62% • Controls = 65% 																								
Histological differentiation																												
	IBT group (moderate dose)	IBT group (high dose)	Control group	Actuarial probability of survival rate for 5 years (Kaplan–Meier) by Dukes' stage <table border="1"> <thead> <tr> <th></th> <th>A</th> <th>B</th> <th>C</th> <th>D</th> </tr> </thead> <tbody> <tr> <td>High dose</td> <td>100%</td> <td>33%</td> <td>40%</td> <td>25%</td> </tr> <tr> <td>Moderate dose</td> <td>97%</td> <td>94%</td> <td>51%</td> <td>29%</td> </tr> <tr> <td>Controls</td> <td>100%</td> <td>78%</td> <td>50%</td> <td>13%</td> </tr> </tbody> </table>			A	B	C	D	High dose	100%	33%	40%	25%	Moderate dose	97%	94%	51%	29%	Controls	100%	78%	50%	13%			
	A	B	C			D																						
High dose	100%	33%	40%	25%																								
Moderate dose	97%	94%	51%	29%																								
Controls	100%	78%	50%	13%																								
Well	46% (44/96)	84% (16/19)	66% (76/115)*																									
Moderate	46% (44/96)	11% (2/19)	27% (31/115)†																									
Poorly	6% (6/96)	0	2% (2/115)																									
Mucinous	2% (2/96)	5% (1/19)	4% (5/115)																									
Others	0	0	1% (1/115)																									
* p = 0.003, † p = 0.004																												
Indications: Middle or lower rectal cancer, of variable Dukes' stage																												
Technique: Remote afterloader was used (RAL-30A or RAL-40A, Toshiba, Tokyo, Japan) with Cobalt-60 source. Single doses ranged from 4 Gy to 40 Gy and total doses from 16 Gy to 80 Gy. Surgery was performed 2 weeks after IBT																												
Median follow-up (months):																												
<ul style="list-style-type: none"> • Moderate dose IBT = 49.5 (range 8.6–60) • High dose IBT = 60 (range 6–60) • Control group = 47.5 (range 9.2–60) 																												
Disclosure of interest: Not stated																												

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<p>Kusunoki M (1997)²</p> <p>Case series</p> <p>Japan</p> <p>Study period: 1986–1995</p> <p>n = 106</p> <p>Population: 106 patients with rectal cancer treated with preoperative IBT and surgery</p> <ul style="list-style-type: none"> 82% (87/106) moderate dose IBT 18% (19/106) high dose IBT <p>Median age (years):</p> <ul style="list-style-type: none"> Moderate dose IBT = 59 (range 25–87) High dose IBT = 65 (range 46–86) <table border="1"> <thead> <tr> <th>Dukes' stage</th> <th>IBT group (moderate dose)</th> <th>IBT group (high dose)</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>30% (26/87)</td> <td>37% (7/19)</td> </tr> <tr> <td>B</td> <td>22% (19/87)</td> <td>21% (4/19)</td> </tr> <tr> <td>C</td> <td>48% (42/87)</td> <td>42% (8/19)</td> </tr> <tr> <td>D</td> <td>0%</td> <td>0%</td> </tr> </tbody> </table> <p>Histological differentiation</p> <table border="1"> <thead> <tr> <th></th> <th>IBT group (moderate dose)</th> <th>IBT group (high dose)</th> </tr> </thead> <tbody> <tr> <td>Well</td> <td>47% (41/87)</td> <td>84% (16/19)</td> </tr> <tr> <td>Moderate</td> <td>45% (39/87)</td> <td>11% (2/19)</td> </tr> <tr> <td>Poorly</td> <td>6% (5/87)</td> <td>0</td> </tr> <tr> <td>Mucinous</td> <td>2% (2/87)</td> <td>5% (1/19)</td> </tr> </tbody> </table> <p>Indications: Rectal cancer (not otherwise specified)</p> <p>Technique: As for Yanagi et al.</p> <p>Follow-up: 0.5–9 years</p> <p>Disclosure of interest: Not stated</p> <p>IP overview: Preoperative high dose rate brachytherapy for rectal cancer</p>	Dukes' stage	IBT group (moderate dose)	IBT group (high dose)	A	30% (26/87)	37% (7/19)	B	22% (19/87)	21% (4/19)	C	48% (42/87)	42% (8/19)	D	0%	0%		IBT group (moderate dose)	IBT group (high dose)	Well	47% (41/87)	84% (16/19)	Moderate	45% (39/87)	11% (2/19)	Poorly	6% (5/87)	0	Mucinous	2% (2/87)	5% (1/19)	<p>Sphincter saving resection</p> <ul style="list-style-type: none"> High dose IBT = 63% (12/19) Moderate dose IBT = 74% (64/87) <p>The paper states that IBT did not affect the surgical procedure or the postoperative course of patients who underwent restorative surgery.</p>	<p>Complications requiring treatment</p> <p>Fistula formation</p> <ul style="list-style-type: none"> High dose = 16% (3/19) Moderate dose = 5% (4/87) <p>Anastomotic dehiscence</p> <ul style="list-style-type: none"> High dose = 0% (0/19) Moderate dose = 5% (4/87) <p>Pelvic sepsis</p> <ul style="list-style-type: none"> High dose = 11% (2/19) Moderate dose = 2% (2/87) <p>Wound sepsis</p> <ul style="list-style-type: none"> High dose = 5% (1/19) Moderate dose = 3% (3/87) <p>Small bowel perforation</p> <ul style="list-style-type: none"> High dose = 11% (2/19) Moderate dose = 0% (0/87) <p>Small bowel obstruction</p> <ul style="list-style-type: none"> High dose = 11% (2/19) Moderate dose = 7% (6/87) <p>(All were successfully treated without surgery)</p> <p>Colonic pouch complication</p> <ul style="list-style-type: none"> High dose = 5% (1/19) Moderate dose = 6% (5/87) <p>Perianal skin complication</p> <ul style="list-style-type: none"> High dose = 32% (6/19) Moderate dose = 17% (15/87) <p>Anastomotic stricture</p> <ul style="list-style-type: none"> High dose = 0% (0/19) Moderate dose = 3% (3/87) <p>Radiation colitis</p> <ul style="list-style-type: none"> High dose = 0% (0/19) Moderate dose = 1% (1/87) <p>Stoma complication</p> <ul style="list-style-type: none"> High dose = 0% (0/19) Moderate dose = 1% (1/87) <p>Cerebral infarction</p> <ul style="list-style-type: none"> High dose = 5% (1/19) Moderate dose = 0% (0/87) <p>12 patients required surgical intervention for complications.</p>	<p>Consecutive recruitment of patients.</p> <p>Same study centre as Yanagi et al.</p> <p>'Moderate' and 'high' dose relates to the total dose of radiation rather than the dose rate.</p> <p>Although the paper does not state that this is high dose rate brachytherapy, it is cited as being so by Vuong et al.</p> <p>The authors state that they abandoned the use of high-dose IBT in 1988 due to patients being left with poor sphincter function. A letter published by the same authors states that they subsequently used more moderate doses of radiation (30–40 Gy) at the same dose rate (see Appendix A).</p> <p>From the absence of Dukes' stage D patients it can be assumed that treatment intent was curative, although this is not explicitly stated.</p>
Dukes' stage	IBT group (moderate dose)	IBT group (high dose)																															
A	30% (26/87)	37% (7/19)																															
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Abbreviations used: EBRT, external beam radiation therapy; HDR, high dose rate; IBT, intraluminal brachytherapy therapy; MRI, magnetic resonance imaging			
Study details	Key efficacy findings	Key safety findings	Comments
<p>Vuong T (2002)³, (2005)⁴</p> <p>Case series</p> <p>Canada</p> <p>Study period: October 1998 – April 2001</p> <p>n = 49</p> <p>Population: 49 patients with locally advanced but resectable rectal cancer</p> <p>Median age = 69 years (range 48–92)</p> <p>Indications:</p> <p>Inclusion criteria: Resectable rectal adenocarcinoma with the upper margin within 15 cm of the anal verge, defined as bulky T2, T3 or early T4 tumour</p> <p>Exclusion criteria: Small T2 tumours with favourable features that could be treated with local excision; abdominal nodal disease; metastases; previous history of pelvic radiation or prostate implants</p> <p>Technique: Dedicated inflatable endorectal applicator was used (Novi Sad, Nucletron BV, Veenendaal, the Netherlands). Daily dose of 6.5 Gy over 4 consecutive days. Radio-opaque clips were used to mark the position of the tumour. Surgery was performed 4–8 weeks after brachytherapy</p> <p>If necessary, EBRT was given after surgery with chemotherapy. All patients with positive nodes were given postoperative adjuvant chemotherapy and EBRT</p>	<p>Complete clinical response (no tumour defined as no macroscopic disease seen at the time of surgery) = 64% (30/47)</p> <p><i>Tumour in lower third of rectum (n = 24)</i></p> <p>Initial tumour size 3–5 cm (n = 13):</p> <ul style="list-style-type: none"> No tumour = 9 patients Residual tumour = 4 patients <p>Initial tumour size > 5–9 cm (n = 9):</p> <ul style="list-style-type: none"> No tumour = 5 patients Residual tumour = 4 patients <p>Initial tumour size > 9 cm (n = 2):</p> <ul style="list-style-type: none"> No tumour = 1 patient Residual tumour = 1 patient <p><i>Tumour in middle third of rectum (n = 22)</i></p> <p>Initial tumour size 3–5 cm (n = 9):</p> <ul style="list-style-type: none"> No tumour = 7 patients Residual tumour = 2 patients <p>Initial tumour size > 5–9 cm (n = 13):</p> <ul style="list-style-type: none"> No tumour = 8 patients Residual tumour = 5 patients <p><i>Tumour in upper third of rectum (n = 3)</i></p> <p>Initial tumour size 3–5 cm (n = 3):</p> <ul style="list-style-type: none"> No tumour = 0 patients Residual tumour = 3 patients 	<p><i>Radiation toxicity</i></p> <p>Rectal perforation = 0% (0/49)</p> <p>Grade 2 proctitis = 100% (49/49)</p> <p>Grade 3 dermatitis = 4% (2/49)</p> <p>In 9 patients, proctitis symptoms persisted for 6–10 weeks after surgery. Most patients improved preoperatively with medication (5 patients required morphine).</p> <p>There were no hospital admissions for toxicity during the study.</p> <p><i>Postoperative complications</i></p> <p>In one case, there was no identifiable lesion at the time of surgery and inadvertently resection was performed through the tumour. An early recurrence was observed two months after surgery.</p> <p>One patient developed a perirectal abscess, possibly attributable to preoperative India ink injection to provide landmarks for the surgeon.</p> <p>Intraoperative bleeding > 1500 ml = 6% (3/49)</p> <p>Bladder dysfunction = 8% (4/49) (one patient still required catheterisation at 20 months).</p>	<p>Initial assessment of tumour was performed using MRI, whereas the residual tumour was measured from the surgical specimen.</p> <p>Two patients refused their planned abdominal perineal resection after an endoscopic-guided rectal ultrasound revealed normal findings a week before surgery was due. At 40 and 27 months, they were still being followed up and doing well.</p>

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<p>Vuong T (2002) (2005) <i>contd</i></p> <p>Median follow-up: 29 months (range 16–46)</p> <p>Disclosure of interest: Not stated</p>	<table border="1"> <thead> <tr> <th>Stage</th> <th>Initial clinical stage</th> <th>Pathologic stage (postoperative)</th> </tr> </thead> <tbody> <tr> <td>T0</td> <td>0</td> <td>15</td> </tr> <tr> <td>T1</td> <td>0</td> <td>8</td> </tr> <tr> <td>T2</td> <td>3</td> <td>9</td> </tr> <tr> <td>T3</td> <td>42</td> <td>15</td> </tr> <tr> <td>T4</td> <td>4</td> <td>0</td> </tr> <tr> <td>N0</td> <td>33</td> <td>35</td> </tr> <tr> <td>N1–2</td> <td>16</td> <td>14</td> </tr> </tbody> </table> <p>Five patients developed liver metastases (3 were found at laparotomy, 2 developed 4 and 6 months after completion of adjuvant chemotherapy and EBRT). One patient had isolated local recurrence (time not stated).</p>			Stage	Initial clinical stage	Pathologic stage (postoperative)	T0	0	15	T1	0	8	T2	3	9	T3	42	15	T4	4	0	N0	33	35	N1–2	16	14	<p>Pelvic abscess = 6% (3/49)</p> <p>Anastomotic leak = 4% (2/49)</p> <p>Postoperative fever caused by lung atelectasis = 4% (2/49)</p> <p>Persistent perineal pain = 2% (1/49)</p> <p>Anastomotic stenosis = 4% (2/49)</p>	
Stage	Initial clinical stage	Pathologic stage (postoperative)																											
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IP overview: Preoperative high dose rate brachytherapy for rectal cancer

Abbreviations used: EBRT, external beam radiation therapy; HDR, high dose rate; IBT, intraluminal brachytherapy therapy; MRI, magnetic resonance imaging			
Study details	Key efficacy findings	Key safety findings	Comments
<p>Ishikawa H (2004)⁵</p> <p>Case series</p> <p>Japan</p> <p>Study period: April 1988 – July 1997</p> <p>n = 41</p> <p>Population: 41 patients with rectal cancer</p> <p>Mean age: 61 years (range 27–74)</p> <p>Indications: Rectal cancer located mainly below the pelvic peritoneal reflection; cT3 or cT4 tumour; no distant metastases; no previous chemotherapy, immunotherapy or radiation therapy to the pelvis; younger than 80 years at diagnosis; no pre-existing serious disorders of the heart, lungs, liver or kidneys.</p> <p>Technique: Patients were first treated with extracorporeal irradiation; 30 Gy was delivered in 15 fractions over 3 weeks. Endocavitary radiation was then delivered by a cobalt-60 remote-controlled loading system. A dose of 40 Gy was delivered using a hand-made applicator in four fractions over 2 weeks. The most recent 14 patients received a modified regimen of 40 Gy extracorporeal irradiation and 30 Gy endocavitary irradiation. All patients underwent abdominoperineal resection 2 weeks after completion of radiation treatment. All patients took 5-fluorouracil daily for 1 year after surgery</p> <p>Median follow-up: 79.2 months</p> <p>Disclosure of interest: Not stated</p>	<p>Recurrence = 27% (11/41)</p> <p>Local recurrence = 15% (6/41)</p> <p>Cancer-related deaths = 15% (6/41)</p> <p>Cumulative 5-year survival rate (Kaplan–Meier) = 82.9%</p> <p>Cumulative 5-year disease-free survival rate (Kaplan–Meier) = 71.8%</p> <p>10% (4/41) of surgical specimens showed sterile tumour cells without nodal involvement.</p> <p>Multivariate analysis showed that nodal involvement was the only independent prognostic factor of survival.</p>	<p>Mild to moderate diarrhoea with anal pain = 61% (25/41)</p> <p>Non-haematological postoperative complications = 44% (18/41)</p> <p>Perineal dehiscence = 24% (10/41)</p> <p>Fistula formation = 15% (6/41)</p> <p>Small bowel obstruction = 10% (4/41) (3 required surgical treatment)</p> <p>Chronic cystitis = 5% (2/41)</p>	<p>7 patients who were eligible for the study refused treatment because of the long-term hospitalisation required.</p> <p>Treatment included extracorporeal irradiation as well as endocavitary brachytherapy.</p> <p>The paper states that if surgery had been performed after maximum tumour regression had occurred, the rate of tumour cell sterility might have been higher.</p> <p>The authors state that the outcome of all patients was well documented.</p>

IP overview: Preoperative high dose rate brachytherapy for rectal cancer

Abbreviations used: EBRT, external beam radiation therapy; HDR, high dose rate; IBT, intraluminal brachytherapy therapy; MRI, magnetic resonance imaging			
Study details	Key efficacy findings	Key safety findings	Comments
<p>Jakobsen A (2006)⁶</p> <p>Case series</p> <p>Denmark</p> <p>n = 50</p> <p>Population: 50 patients with locally advanced rectal adenocarcinoma</p> <p>Median age: 61 years</p> <p>Indications:</p> <p>Inclusion criteria: Biopsy-proven adenocarcinoma localised ≤ 10 cm from the anal verge, T3 tumour with circumferential margin ≤ 5 mm on MRI scan, in lower part of rectum with no clear mesorectal fascia and ≤ 5 mm distance to muscles and other organs; World Health Organization performance status ≤ 2; age > 18 years; normal liver, kidney and bone marrow function; sufficient contraception in women with childbearing potential; and informed consent</p> <p>Exclusion criteria: distant metastases; laparotomy within 2 weeks before inclusion; previous pelvic irradiation</p> <p>Technique: Chemoradiation was administered with an endorectal brachytherapy boost. Brachytherapy was given with a Nucletron high-dose-rate afterloading system (Nucletron BV, Veenendaal, the Netherlands) equipped with a nominal 370 GBq (10 Ci) ¹⁹²Ir source. A rigid applicator with a central catheter for the source was used.</p> <ul style="list-style-type: none"> • 48/50 patients underwent surgery after treatment • 46/50 received the planned external radiation • 45/50 received the planned chemotherapy <p>Follow-up: not stated</p> <p>Disclosure of interest: Not stated</p>	<p>Tumour response in 48 operated patients (operative specimens were evaluated according to the Tumor Regression Grade grading system. The grading of effect is based on the relative amount of viable carcinoma cells in relation to irradiation-induced fibrosis).</p> <p>No residual tumour = 27% (13/48) Microscopic tumour only = 27% (13/48) Moderate tumour response = 40% (19/48) Minor response = 8% (4/48)</p>	<p><i>Radiation toxicity</i></p> <p>Leucopenia = 4% (2/50) Thrombocytopenia = 2% (1/50) Grade 3 toxicity = 6% (3/50) Grade 2 toxicity = 24% (12/50)</p> <p><i>Surgical complications</i></p> <p>Wound infection = 6% (3/48) Postoperative ileus = 4% (2/48) Anastomotic leakage = 0% (0/48) Re-operation = 8% (4/48)</p>	<p>Patients were treated with chemotherapy and external radiotherapy as well as HDR brachytherapy.</p> <p>2 patients did not have surgery after chemoradiotherapy treatment.</p>

IP overview: Preoperative high dose rate brachytherapy for rectal cancer

Validity and generalisability of the studies

- In the non-randomised comparative study, 55% of the patients in the control group were treated during the 8-year period preceding the advent of brachytherapy in that centre.¹ Aspects of the operative techniques may have improved over time, and the inclusion of a considerable proportion of surgically treated patients from an earlier era may have introduced bias in favour of the preoperative brachytherapy arm.
- The non-randomised comparative study initially treated patients with a high total dose of brachytherapy but this was later modified to a more moderate dose, delivered at the same dose rate.
- Only one study compared brachytherapy and surgery with surgery alone and this study did not present data on complications in the group of patients treated with surgery alone.¹ It is difficult, therefore, to ascertain what proportion of complications could be attributed to the preoperative brachytherapy rather than the surgery itself.
- Two studies were reported from the same study centre and there is a likely overlap between patients in these two studies.^{1,2}
- In one case series, patients were treated with external beam radiation as well as endocavitary brachytherapy. Without a control group, it is impossible to attribute particular safety and efficacy outcomes to either form of treatment.⁵ In another case series, brachytherapy was administered as a boost after chemotherapy and EBRT.⁶
- Delivery systems and total brachytherapy dose varied between studies.

Specialist advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

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- There is a lack of long-term follow-up data so there are uncertainties about the long-term efficacy.
- HDR brachytherapy may be administered on its own before surgery or as a boost to EBRT or chemoradiotherapy.

IP overview: Preoperative high dose rate brachytherapy for rectal cancer

- Key outcome measures include local tumour control, sphincter-preserving surgery rates, pathological complete remission rates, disease-free and overall survival rates and quality of life (including long-term bowel function).
- Potential adverse effects of the procedure include rectal or bladder perforation, mucosal damage causing ulceration and bleeding, stenosis of the rectal lumen, fistula formation between the rectum and the bladder or the vagina, myocardial infarction and stroke.

Issues for consideration by IPAC

- HDR brachytherapy delivery systems vary in design. There are rigid cylinders with a centreline source and flexible catheters with channels that can be loaded or not to achieve conformal dose delivery.
- In the literature, it is not always clear whether the brachytherapy is high dose rate.
- This overview does not include patients with anal cancer. Most of the literature identified reported outcomes separately for anal cancer.
- Treatment intent (curative or palliative) should be considered. Of the reviewed studies, the great majority of the patients can be assumed to have been treated with a curative intent (and have been treated with resective surgery following brachytherapy). However, there are several studies in the literature reporting the use of the technique in the context of inoperable rectal cancer (see appendix A).

References

1. Yanagi H, Kusunoki M, Kamikonya N et al. (1997) Results of preoperative intraluminal brachytherapy combined with radical surgery for middle and lower rectal carcinomas. *Journal of Surgical Oncology* 65: 76–81.
2. Kusunoki M, Yanagi H, Kamikonya N et al. (1997) Complications after preoperative intraluminal radiotherapy and radical surgery for rectal carcinoma: a review of 100 cases. *Surgery Today* 27: 1103–8.
3. Vuong T, Belliveau PJ, Michel RP et al. (2002) Conformal preoperative endorectal brachytherapy treatment for locally advanced rectal cancer. *Diseases of the Colon and Rectum* 45: 1486–1495.
4. Vuong T, Devic S, Moffah B et al. (2005) High-dose-rate endorectal brachytherapy in the treatment of locally advanced rectal carcinoma: technical aspects. *Brachytherapy* 4: 230–5.
5. Ishikawa H, Fujii H, Koyama F et al. (2004) Long-term results of high-dose extracorporeal and endocavitary radiation therapy followed by abdominoperineal resection for distal rectal cancer. *Surgery Today* 34: 510–17.
6. Jakobsen A, Mortensen JP, Bisgaard C et al. (2006) Preoperative chemoradiation of locally advanced T3 rectal cancer combined with an endorectal boost. *International Journal of Radiation Oncology, Biology, Physics* 64: 461–5.

Appendix A: Additional papers on preoperative high dose rate brachytherapy for rectal cancer not included in the summary table

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article title	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in Table 2
Begum N, Asghar A, Khan N et al.(2003) High dose rate intraluminal brachytherapy in combination with external beam radiotherapy for palliative treatment of cancer rectum. <i>Journal of the College of Physicians & Surgeons – Pakistan</i> 13: 633–6.	15 patients (only 10 completed treatment and were evaluated). 2-month follow-up.	Symptom relief within 1 week. Excellent palliation achieved at end of treatment. Late complications = 10% (1/10) (intestinal obstruction).	Small sample size. Main aim of treatment was palliation.
Harrison L, Minsky B, Enker W et al.(1998) High dose rate intraoperative radiation therapy (HDR-IORT) as part of the management strategy for locally advanced primary and recurrent rectal cancer. <i>International Journal of Radiation Oncology, Biology, Physics</i> 42: 325–30.	68 patients (66 were evaluated). Median follow-up = 17.5 months.	Actuarial local control = 81% for primary cases and 63% for patients with recurrent disease. 2-year actuarial disease-free survival = 69% and 47%, respectively.	High dose rate radiation was delivered intraoperatively via an applicator. Study included 22 patients with primary unresectable disease and 46 patients with recurrent disease.
Hoskin PJ, de Canha SM, Bownes P et al. (2004) High dose rate afterloading intraluminal brachytherapy for advanced inoperable rectal carcinoma. <i>Radiotherapy and Oncology</i> 73: 195–8.	48 patients (26 unfit for surgery, 22 for palliation).	Good symptom control. Median survival = 6 months (range 1–54).	Patients were described as inoperable.
Kuehne J, Kleisli T, Biernacki P et al.(2003) Use of high-dose-rate brachytherapy in the management of locally recurrent rectal cancer. <i>Diseases of the Colon and Rectum</i> 46: 895–9.	27 patients. Mean follow-up = 50 months.	37% (10/27) patients alive at time of report. 18% (5/27) died of non-cancer-related causes without evidence of recurrent disease. 18% (5/27) complications = 3 abscesses, 2 fistulas.	Small sample size. Patients had locally recurrent rectal cancer that could not be completely removed surgically.
Kusunoki M, Shoji Y, Yanagi H et al. (1993) Anorectal function after preoperative intraluminal brachytherapy and colonic J pouch-anal anastomosis for rectal carcinoma. <i>British Journal of Surgery</i> 80: 933–5.	24 patients (8 received no radiation, 8 received 30 Gy, 8 received 80 Gy)	Moderate dose of 30 Gy and anoabdominal rectal resection with colonic J pouch-anal anastomosis provides a good treatment for low rectal cancer.	Same study centre as reference 1 and 2.

Article title	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in Table 2
Kusunoki M, Yanagi H, Kamikonya N et al. (1996) Significant effects of preoperative intraluminal brachytherapy on the survival rate after resection of rectal carcinoma. <i>International Journal of Oncology</i> 9: 645–51.	85 patients.	Preoperative IBT affected tumour morphology and prognosis. Proportion of residual viable cells was significantly correlated to survival.	Same study centre as reference 1 and 2.
Sakurai H, Mitsuhashi N, Harashima K et al. (2004) CT-fluoroscopy guided interstitial brachytherapy with image-based treatment planning for unresectable locally recurrent rectal carcinoma. <i>Brachytherapy</i> 3: 222–30.	18 patients. Follow-up = 14 months.	Brachytherapy needles inserted under CT guidance. 2 patients developed incomplete peroneal nerve palsy after needle removal. 6% (1/18) complete regression.	Patients had locally recurrent rectal cancer and were described as inoperable.
Scott A, Lee C, Myint A (2005) Initial experience with the new Nucletron flexible applicator for HDR brachytherapy in the treatment of early rectal cancer. <i>Radiotherapy and Oncology</i> 76 (Suppl. 2): S137–S138.	5 patients	Flexible applicator allows better treatment geometry and the possibility of treating tumours situated higher in the rectum.	No safety or efficacy data are presented.
Sun Myint A (2005) Brachytherapy in rectal cancer (curative intent) Clatterbridge experience. <i>Radiotherapy and Oncology</i> 75 (Suppl. 1): S17–S18.	9 patients with intent to cure.	Local failure rate = 22% (2/9). Local control after salvage = 100% (9/9)	Conference abstract – limited information.
Yanagi H, Kusunoki M, Kamikonya N (1992) Small-bowel perforation after preoperative high-dose-rate intraluminal brachytherapy for rectal carcinoma. <i>AJR: American Journal of Roentgenology</i> 159: 224.	2 patients.	Small bowel perforation in 3% (2/71) of patients; 1 patient died as a result. Dose was subsequently modified and there have been no more such complications.	Letter describes 2 cases with small bowel perforation out of 71 patients treated. No details of the other patients are given.
Yanagi H, Kusunoki M, Yamamura T (2000) The effectiveness of preoperative intraluminal brachytherapy in preventing wall penetration and nodal involvement of rectal carcinomas. <i>Surgery Today</i> 30: 410–15.	230 patients. (115 treated with IBT and 115 historical controls).	Good local control achieved for T3 stage with IBT, similar to T ≤ 2 in both groups.	Same study as reference 1 and 2 in Table 2. Results compare N+ and N– patients.

Appendix B: Related published NICE guidance for preoperative high dose rate brachytherapy for rectal cancers

Guidance	Recommendation
Cancer Service Guidance	Although the guidance included evidence on preoperative radiotherapy in the treatment of rectal cancer, it did not specifically mention brachytherapy. The guideline states that preoperative radiotherapy reduces the risk of local recurrence and may improve 5-year survival rates. However, there is significant morbidity so careful patient selection is important.

**Appendix C: Literature search for preoperative high dose rate
brachytherapy for rectal cancer**

Procedure number: 342	Procedure name: Brachytherapy for rectal cancers	
Databases	Version searched (if applicable)	Date searched
The Cochrane Library	2005 Issue 4	30/11/2005
CRD	November 2005	30/11/2005
EMBASE	1980 to 2005 Week 47	30/11/2005
Medline	1966 to November Week 3 2005	30/11/2005
PreMedline	30 November 2005	30/11/2005
CINAHL	1982 to November Week 3 2005	30/11/2005
British Library Inside Conferences (limited to current year only)	1993 to date	30/11/2005
National Research Register	2005 Issue 4	30/11/2005
Controlled Trials Registry	N/A	30/11/2005

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in other databases.

- 1 BRACHYTHERAPY/
- 2 brachytherap\$.tw.
- 3 (internal radiotherap\$ or internal radiation therap\$).tw.
- 4 (intracavit\$ radiotherap\$ or intracavit\$ radiation therap\$).tw.
- 5 (implant therap\$ or implant radiation therap\$).tw.
- 6 (interstitial radiotherap\$ or interstitial radiation therap\$).tw.
- 7 iodine-125 seed\$.tw.
- 8 or/1-7
- 9 *Rectal Neoplasms/
- 10 (rect\$ adj2 (cancer\$ or neoplasm\$ or lesion\$ or tumour\$ or tumor\$ or malignan\$ or carcinoma\$)).tw.
- 11 *Anus Neoplasms/
- 12 (anus adj2 (cancer\$ or neoplasm\$ or lesion\$ or tumour\$ or tumor\$ or malignan\$ or carcinoma\$)).tw.
- 13 (anal adj2 (cancer\$ or neoplasm\$ or lesion\$ or tumour\$ or tumor\$ or malignan\$ or carcinoma\$)).tw.
- 14 or/9-13
- 15 8 and 14
- 16 Animals/
- 17 Humans/
- 18 16 not (16 and 17)
- 19 15 not 18