NATIONAL INSTITUTE FOR HEALTH AND CARE 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 that affects the rectum (end part of the bowel). In preoperative high dose rate brachytherapy radioactive material is put within, or close to, the cancer to shrink it before surgery.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make 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 IP overview was prepared in December 2014.

Procedure name

- Preoperative high dose rate brachytherapy for rectal cancer
- Endorectal high dose rate (HDR) brachytherapy
- HDR afterloading brachytherapy
- Intraluminal HDR brachytherapy

Specialist societies

- Association of Coloproctology of Great Britain and Ireland
- Royal College of Radiologists − Faculty of Clinical Oncology

Description

Indications and current treatment

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.

Surgery is the main treatment for patients with rectal cancer who can be treated with curative intent. It involves resection of the affected part of the rectum with the mesorectum. The anal sphincter is preserved wherever possible: a colostomy is formed when this is not possible.

In some patients, radiotherapy and/or chemotherapy are used before, during or after surgery in an attempt 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 the placement of 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 into the surrounding tissue.

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 treatments than with low dose rate treatments.

High dose rate (HDR) brachytherapy is sometimes used as a boost after EBRT for advanced rectal cancer, to improve local control and control symptoms. It is also used on its own before surgery in patients with cancer in the middle or lower third of the rectum. The aim of preoperative HDR rectal brachytherapy is to shrink (down-stage) the tumour, which may make anal preservation surgery feasible for more patients.

What the procedure involves

Endorectal HDR brachytherapy for rectal cancer is usually carried out under sedation. Before treatment the tumour size and stage are determined using imaging techniques, and a 3-dimensional CT-based treatment planning system may be used to guide source positioning and appropriate dosing. Radio-opaque clips may be placed to mark the margins of the tumour, using proctoscopy or sigmoidoscopy.

A rigid or flexible endorectal applicator is used to deliver radiation to the tumour within the rectum. A balloon may be placed over the applicator to displace the

uninvolved rectal mucosa away from the radioactive source to reduce toxicity. When the balloon is inflated, it immobilises the applicator and also helps to facilitate close contact with the tumour. Catheters within the applicator are subsequently loaded with the radioactive source (this is sometimes called ‘afterloading’), according to the treatment plan.

A few weeks after completion of brachytherapy, residual tumour is removed surgically.

Outcome measures and disease classification

Colorectal cancer classification

The Tumour Node Metastasis (TNM) classification system for malignant tumours is used to describe the stage of a cancer. ‘T’ describes the size and location of the primary tumour, including whether it has invaded surrounding tissue. ‘N’ describes the extent of which the cancer has spread to local/regional lymph nodes. ‘M’ describes the degree of distant metastasis. The following classification applies to colorectal cancer:

- T0: There is no evidence of colorectal cancer
- T1: The tumour has grown into the submucosa
- T2: The tumour has grown into the muscularis propria
- T3: The tumour has grown through the muscularis propria into pericolorectal tissues
- T4a: The tumour penetrates the surface of the visceral peritoneum, meaning that it has grown through all layers of the colon
- T4b: The tumor has grown into or has attached to other organs or structures.

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 1 lymph node in the area, and stage D refers to cancer that has spread to another organ in the body.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to preoperative high dose rate brachytherapy for rectal cancer. Searches were conducted of the following databases, covering the period from their commencement to 20 November 2014: 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). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection 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, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with rectal cancer.
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 IP overview

This IP overview is based on approximately 1900 patients from 1 randomised controlled trial (described in 2 reports), 5 non-randomised comparative studies, and 3 case series [1–9] .

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.

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

Study 1 Jakobsen A (2012)

Details

Study type	**Randomised controlled trial**
Country	Denmark and Canada
Recruitment period	2005–10
Study population and number	**n=243 (120 HDR brachytherapy boost versus 123 standard chemoradiation therapy)** Patients with locally advanced resectable rectal cancer (T3: 204; T4: 39).
Age and sex	Age range: 35–78 (median 64 versus 62 years) 64% (156/243) male
Patient selection criteria	Histopathological verification of adenocarcinoma, resectability, distance <10 cm from the anal verge, circumferential margin <5 mm on MRI, performance status ≤2. Exclusion criteria included previous malignant disease or pelvic radiotherapy.
Technique	All patients received external beam radiotherapy, given with a linear accelerator using 3-dimensional conformal planning. Endorectal brachytherapy was given with an applicator. A 5 Gy dose was prescribed to a 10 mm distance from the applicator surface and was planned to provide a uniform dose distribution along the tumour central axis. The treatment was scheduled for weeks 4 and 6 in the treatment course. Concomitant chemotherapy was added to both arms on treatment days. Surgery was done 8 weeks after the end of treatment, based on total mesorectal excision surgery. The treating surgeon determined the operation type. The paper does not specify what device was used but a previous article from the same centre states that brachytherapy was given with a Nucletron high-dose-rate afterloading system (Nucletron BV, Veenendaal, the Netherlands).
Follow-up	**Not reported**
Conflict of interest/source of funding	None

Analysis

Study design issues:
Patients were randomly allocated to receive 50.4 Gy in 28 fractions or the same treatment supplemented with 10 Gy in 2 fractions of endorectal brachytherapy. Those patients who were not eligible for brachytherapy were prescribed an external radiotherapy boost of 12 Gy delivered in 2 Gy/fraction to the gross tumour volume (equivalent to 2 fractions of brachytherapy), 5 Gy/fraction; this was necessary for 17 patients.

An additional 5 patients were randomised but were ineligible. Of the 248 randomised patients, 93% (n=231) received the planned radiotherapy with no difference between the 2 groups. A total of 8 patients stopped treatment because of toxicity (4 in each group), 1 patient died of non-treatment/non-cancer related reasons, 1 patient refused treatment and 2 patients withdrew for other reasons.

The rate of complete pathological remission was the primary endpoint.

The study was planned to detect a difference in the complete pathological remission rate between the 2 groups of 15%.

Study population issues:
There were no statistically significant differences in baseline characteristics between the groups. Most patients (84%) had T3 tumours, and 88% had clinical lymph node metastases. 92% of the tumours were in the lower third of the rectum.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **243 (120 vs 123)**

12 patients (6 in each treatment group) did not receive the planned preoperative treatment (8 stopped because of toxicity, 1 died from unrelated causes, 1 refused treatment and 2 for unspecified other reasons).

Curative surgery

- HDR brachytherapy boost=93% (106/114) (3 patients had preoperative progression of disease with distant metastases, curative operation was not possible in 1 patient, 2 patients died in relation to the surgery [not further described], 1 patient refused surgery and 1 patient did not have surgery for other reasons)
- Standard chemoradiotherapy=93% (109/117) (5 patients had preoperative progression of disease with distant metastases, curative operation was not possible in 1 patient,1 patient refused surgery and 1 patient did not have surgery for other reasons)

Complete pathological remission rate by intention to treat (all tumours)

- HDR brachytherapy boost=18%
- Standard chemoradiotherapy=18%

Secondary endpoints for T3 tumours (patients who received curative surgery)

Variable	**HDR brachytherapy boost n=90**	**Standard chemo-radiotherapy n=92**	**p value**
R0 resection	99% (n=87)	90% (n=83)	0.03
Major response (tumour regression grade, 1+2)	44% (35/80)	28% (23/82)	0.04
Major response according to tumour diameter			
<3.7 cm	58% (n=23)	33% (n=14)	<0.03
>3.7 cm	31% (n=11)	28% (n=8)	Not significant

Safety

Toxicity grade 2 or more, n (%)

	HDR brachytherapy boost	**Standard chemo-radiotherapy**
Thrombocyto-paenia	0 (0)	0 (0)
Neutropaenia	1 (1)	1 (1)
Nausea	7 (6)	5 (4)
Vomiting	2 (2)	3 (2)
Stomatitis	2 (2)	0 (0)
Diarrhoea	23 (19)	23 (19)
Skin	24 (20)	21 (17)
Dysuria	7 (6)	8 (7)
Proctitis	22 (18)	18 (15)

Postoperative complications, n (%)

	HDR brachytherapy boost	**Standard chemo-radiotherapy**
None	71 (67)	61 (56)
Reoperation	5 (5)	9 (8)
Ileus	0 (0)	5 (5)
Infection (related to wound)	16 (15)	12 (11)
Death (due to cardiac complications)	1 (1)	0 (0)
Anastomotic leakage	0 (0)	4 (4)
Fistula	1 (1)	2 (2)
Stenosis	0 (0)	0 (0)
Urinary problems	3 (3)	9 (8)
Other	9 (8)	7 (6)

Abbreviations used: HDR, high dose rate

Study 2 Appelt A (2014)

Details

Study type	**Randomised controlled trial (same trial as Jakobsen A et al, 2012)**
Country	Denmark
Recruitment period	2005–8
Study population and number	**n=221 (110 HDR brachytherapy boost versus 111 standard chemoradiation therapy)** Patients with locally advanced resectable rectal cancer.
Age and sex	Age range: 35–78 (median 64 versus 62 years) 63% (140/221) male
Patient selection criteria	Histopathological verification of adenocarcinoma, resectability, distance<10 cm from the anal verge, circumferential margin<5 mm on MRI, performance status≤2. Exclusion criteria included previous malignant disease or pelvic radiotherapy.
Technique	All patients received external beam radiotherapy, given with a linear accelerator using 3-dimensional conformal planning. Endorectal brachytherapy was given with an applicator. A 5 Gy dose was prescribed to a 10 mm distance from the applicator surface and was planned to provide a uniform dose distribution along the tumour central axis. The treatment was scheduled for weeks 4 and 6 in the treatment course. Concomitant chemotherapy was added to both arms on treatment days. Surgery was done 8 weeks after the end of treatment, based on total mesorectal excision surgery. The treating surgeon determined the operation type. The paper does not specify what device was used but a previous article from the same centre states that brachytherapy was given with a Nucletron high-dose-rate afterloading system (Nucletron BV, Veenendaal, the Netherlands).
Follow-up	**Median 5.4 years**
Conflict of interest/source of funding	None

Analysis

Study design issues:
Longer follow-up of the trial reported by Jakobsen et al. 2012, (study 1).

Patients were randomly allocated to receive 50.4 Gy in 28 fractions or the same treatment supplemented with 10 Gy in 2 fractions of endorectal brachytherapy. Those patients who were not eligible for brachytherapy were prescribed an external radiotherapy boost of 12 Gy delivered in 2 Gy/fraction to the gross tumour volume (equivalent to 2 fractions of brachytherapy), 5 Gy/fraction; this was necessary for 17 patients.

The pathologist scoring for tumour response was blinded to treatment allocation.

Study population issues:
There were no statistically significant differences in baseline characteristics between the groups. Most patients (84%) had T3 tumours, and 89% had clinical lymph node metastases.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **221 (110 vs 111)** **Disease relapse** • HDR brachytherapy boost=35.5% (39/110) • Standard chemoradiotherapy=32.4% (36/111), p value not reported **Mortality** • HDR brachytherapy boost=32.7% (39/110) • Standard chemoradiotherapy=38.7% (43/111), p value not reported **Overall survival at 2 years** • HDR brachytherapy boost=84.5% • Standard chemoradiotherapy=82.0%, p value not reported **Overall survival at 5 years** • HDR brachytherapy boost=63.6% • Standard chemoradiotherapy=70.6%, p=0.34 **Progression-free survival at 2 years** • HDR brachytherapy boost=68.7% • Standard chemoradiotherapy=73.0%, p value not reported **Progression-free survival at 5 years** • HDR brachytherapy boost=52.0% • Standard chemoradiotherapy=63.9%, p=0.32 **Freedom from locoregional failure at 5 years** • HDR brachytherapy boost=85.7% • Standard chemoradiotherapy=93.9%, p=0.06 **Freedom from distant metastases at 2 years** • HDR brachytherapy boost=77.6% • Standard chemoradiotherapy=76.8%, p value not reported **Freedom from distant metastases at 5 years** • HDR brachytherapy boost=68.4% • Standard chemoradiotherapy=68.7%, p=0.85 **5-year risk of secondary cancer** • HDR brachytherapy boost=8.9% • Standard chemoradiotherapy=7.8%, p=0.61 There was no difference in the prevalence of stoma between the groups (66.1% among 2-year survivors and 64.5% among 5-year survivors).	No safety outcomes were reported.
Abbreviations used: HDR, high dose rate	

Study 3 Tunio MA (2010)

Details

Study type	**Prospective non-randomised controlled trial**
Country	Pakistan
Recruitment period	2008–9
Study population and number	**n=36 (17 high dose rate intraluminal brachytherapy versus 19 external beam radiotherapy)** Patients with locally advanced rectal cancer (T3 or above or N+)
Age and sex	Median 35 years (range 17–55) 75% (27/36) male
Patient selection criteria	Histologically proven rectal adenocarcinoma; distal margin of tumour located within 10 cm of the anal verge on endoscopy; T stage≥T3 or nodes positive on preoperative imaging (CT, MRI) and M0; Eastern Cooperative Oncology Group performance status 0–2; normal haematological parameters, normal hepatic parameters, and normal renal function. Patients who had received prior chemotherapy or pelvic radiotherapy or with poor functional status and severe comorbidities were excluded.
Technique	All patients had preoperative external beam radiation therapy plus concomitant chemotherapy given on radiation days. For patients receiving a boost to the gross tumour volume with high dose rate brachytherapy, a single channel catheter with interchangeable shields was used (Flexitron® remote afterloading unit). Brachytherapy was given in 2 sessions (dose 5.5–7 Gy x2). Control patients were given a boost to the gross tumour volume with 3 sessions of external beam radiotherapy (dose 1.8 Gy x3). Patients were assessed for surgery 8 and 10 weeks after the completion of chemoradiation. The choice of procedure was at the discretion of the surgeon.
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues:
The study was described as a randomised controlled trial but the patients were allocated to treatment groups according to their own choice as to whether to receive high dose rate brachytherapy.

The primary endpoint was pathological response rate.

Study population issues:
There were no differences between the 2 treatment groups with regard to mean age, gender, baseline TNM stage, site of primary tumour and performance scale.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **36 (17 versus 19)**

Radiological response - median tumour volume reduction rate:

- HDR brachytherapy boost=68.2%
- Controls=66.0%, p=not significant

Pathological response, n (%)

Stage	HDR brachytherapy boost n=17	Controls n=19	p value
yp T stage			
ypT0	10 (58.8)	3 (15.8)	0.0001
ypT1	3 (17.6)	6 (31.6)	not reported
ypT2	1 (5.9)	4 (21)	not reported
ypT3	2 (11.8)	5 (26.3)	not reported
ypT4	1 (5.9)	1 (5.3)	not reported

Sphincter preservation

- HDR brachytherapy boost=70.6% (12/17)
- Controls=57.9% (11/19), p=0.04

Safety

Toxicity profiles (grade 3 or worse)

Type of toxicity	HDR brachytherapy boost n=17	Controls n=19	p value
Haematological			0.3
Leucopaenia	2 (11.7)	2 (10.5)	not reported
Neutropaenia	2 (11.7)	2 (10.5)	not reported
Thrombocytopaenia	1 (5.9)	1 (5.3)	not reported
Non-haematological			
Hand-foot syndrome	1 (5.9)	1 (5.3)	not reported
Nausea/vomiting	3 (17.6)	5 (26.3)	0.02
Diarrhoea	7 (41.2)	5 (26.3)	0.001
Rectal pain	12 (70.6)	4 (21.1)	0.001
Wound complications	2 (11.8)	3 (15.8)	not reported
Cystitis	2 (11.8)	3 (15.8)	not reported

Abbreviations used: HDR, high dose rate

Study 4 Smith JA (2012)

Details

Study type	**Prospective non-randomised controlled trial**
Country	USA
Recruitment period	2010–2
Study population and number	**n=32 (7 high dose rate brachytherapy versus 14 3D conformal radiotherapy versus 11 intensity-modulated radiotherapy)** Patients with locally advanced low rectal adenocarcinoma
Age and sex	Mean age 60 versus 58 versus 52 years 0% versus 29% versus 64% male
Patient selection criteria	Age>18 years; histologically confirmed adenocarcinoma of the rectum, able to undergo local staging by MRI or endoscopic ultrasound scan demonstrating a T2N1 or T3No-1 tumour; ECOG performance status of 0 or 1. Patients were excluded if they had tumours greater than 12 cm from the anal verge, metastatic disease, positive inguinal or iliac lymph nodes, concurrent malignancy, bulky tumours, or previous pelvic irradiation.
Technique	High dose rate brachytherapy: 4 consecutive daily fractions of 6.5 Gy were delivered using a flexible applicator (OncoSmart, Nucletron, the Netherlands). Conventional chemoradiotherapy: 28 daily fractions of 1.8 Gy over a period of 5 to 6 weeks (total dose of 50.5 Gy) with concurrent chemotherapy.
Follow-up	**Median 7 versus 15 versus 12 months**
Conflict of interest/source of funding	None reported

Analysis

Study design issues:
Only data on brachytherapy were obtained prospectively; data for the control patients were obtained retrospectively.

Historical controls were obtained by identifying all patients with stage 2 or 3 rectal carcinoma who received conventional neoadjuvant chemoradiation at the centre between 2008–12 and went on to surgical resection.

The median lengths of follow up varied between treatment groups.

Study population issues:
Demographic and baseline disease characteristics, including age, race, ECOG performance status, pre-radiotherapy carcinoembryonic antigen (CEA) level, pre-radiotherapy tumour volume, T stage, N stage, and tumour distance from the anal verge, were similar between the 3 groups. There was a significant difference in the gender distribution with 100% of patients in the brachytherapy group being female, compared to 29% and 64% in the other 2 groups (p=0.007).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **32 (7 versus 14 versus 11)**

Sphincter preserving surgery
- HDR brachytherapy=86% (6/7)
- 3DRT=93% (13/14)
- IMRT=91% (10/11), p=0.87

Survival rate at 6 months
- HDR brachytherapy=100% (7/7)
- 3DRT=100% (14/14)
- IMRT=100% (11/11), p=1.0

Local recurrence at 6 months
- HDR brachytherapy=0% (0/7)
- 3DRT=0% (0/14)
- IMRT=0% (0/11), p=1.0

Distant metastases at 6 months
- HDR brachytherapy=0% (0/7)
- 3DRT=7% (1/14)
- IMRT=9% (1/11), p=0.73

Radiological outcomes (for all patients who had MRI studies before and after treatment)

	HDR brachytherapy	3DRT	IMRT	p value
Complete response	14% (1/7)	0% (0/14)	14% (1/7)	0.46
Partial response	57% (4/7)	90% (9/10)	86% (6/7)	0.23
Stable disease	29% (2/7)	10% (1/14)	0% (0/7)	0.26

Pathological outcomes

	HDR brachytherapy	3DRT	IMRT	p value
Complete response	43% (3/7)	7% (1/14)	18% (2/11)	0.06
Positive margins at surgery	0% (0/7)	7% (1/14)	0% (0/11)	0.47
lymph node involvement at surgery	43% (3/7)	57% (8/14)	36% (4/11)	0.57
lymphovascular invasion	14% (1/7)	7% 91/14)	18% (2/11)	0.60

Safety

	HDR brachytherapy	3DRT	IMRT	p value
grade 1 toxicity	57% (4/7)	100% (14/14)	82% (9/11)	0.025
grade 2 toxicity	14% (1/7)	57% (8/14)	18% (2/11)	0.056
grade 3 toxicity	14% (1/7)	7% (1/14)	9% (1/11)	0.87
Postoperative complications	29% (4/7)	36% (4/14)	29% (2/7)	0.90

All grade 3 toxicity complications were proctitis.

Abbreviations used: 3DRT, 3D conformal radiotherapy; HDR, high dose rate; IMRT, intensity-modulated radiotherapy

Study 5 Hesselager C (2013)

Details

Study type	**Non-randomised comparative study**
Country	Canada, Sweden
Recruitment period	1995–2010
Study population and number	**n=954 (318 HDR vs 318 short-course radiotherapy vs 318 surgery alone)** Patients with resectable rectal adenocarcinoma
Age and sex	Age range 31–92 (mean 66, 66, 68 years) 71% (681/954) male
Patient selection criteria	Resectable rectal adenocarcinoma within 15 cm from the anal verge, as measured using a rigid sigmoidoscope.
Technique	HDR brachytherapy treatment was given daily over 4 days (6.5 Gy), followed by surgery after 4–8 weeks. Control patients received either external beam radiotherapy (5 Gy daily, over 5 days) followed by surgery the following week, or no preoperative radiotherapy.
Follow-up	**30 days**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues:
Patients treated in Canada between 1998 and 2010 were matched (gender, age, tumour height and stage) with controls from the Swedish Rectal Cancer Register, treated between 1995 and 2010.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **954 (318 vs 318 vs 318)**

Perioperative data

	HDR brachy n=318	short course RT n=318	surgery only n=318	p value HDRBT/SCRT
Curative surgery, as judged by surgeon	316 (99.4%)	296 (93.1%)	290 (91.2%)	0.4
Anterior resection	171 (53.8%)	159 (50.0%)	159 (50.0%)	0.06
Abdomino-perineal excision	141 (44.3%)	131 (41.2%)	125 (39.3%)	0.4
Hartmann's procedure	6 (1.9%)	28 (8.8%)	34 (10.7%)	0.0002
Laparoscopic	39 (12.3%)	5 (1.6%)	8 (2.5%)	<0.0001

Complete pathological response (ypT0N0) for patients treated by HDR brachytherapy=23.6% (75/318)

Histopathological margins

Resection margin	HDR brachy n=318	short course RT n=318	surgery only n=318	p value HDRBT/SCRT
R0	307 (96.5%)	265 (83.3%)	236 (74.2%)	0.5
R1	8 (2.5%)	9 (2.8%)	13 (4.1%)	0.8
R2	2 (0.6%)	14 (4.4%)	15 (4.7%)	0.0005
Missing	1	30	54	

Safety

Complications

	HDR brachy n=318	short course RT n=318	surgery only n=318	p value HDRBT/SCRT
Perioperative complications				
Rectal perforation	13 (4.1%)	8 (2.5%)	25 (7.8%)	0.1
Perioperative bleeding (mean, ml)	379.3	947.2	918.9	<0.0001
Postoperative complications within 30 days				
Death	3 (0.9%)	1 (0.3%)	7 (2.2%)	Not reported
Cardiovascular	30 (9.4%)	10 (3.1%)	23 (7.2%)	0.002
Infection	30 (9.4%)	26 (8.2%)	20 (6.3%)	0.2
Surgery related overall	87 (27.4%)	87 (27.4%)	71 (22.3%)	0.3
Wound infection	29	39	19	0.25
Intraabdominal infection	12	8	9	0.4
Anastomotic dehiscence	13	20	13	0.2
Wound dehiscence	9	8	5	0.4
Reoperation	13 (4.1%)	45 (14.2%)	39 (12.3%)	0.0005

Abbreviations used: HDR, high dose rate; HDRBT, high dose rate brachytherapy; SCRT, short course radiotherapy

Study 6 Vuong T (2010)

Details

Study type	**Case series**
Country	Canada
Recruitment period	1998–2008
Study population and number	**n=285** Patients with invasive and resectable rectal cancer (T3: 271; T4: 6; T2: 48).
Age and sex	Median 68 years
Patient selection criteria	Patients with enlarged extramesorectal nodes and partially obstructing or obstructing lesions were excluded.
Technique	The paper does not specify what device was used but previous articles from the same centre state that a dedicated inflatable endorectal applicator was used (Novi Sad, Nucletron BV, Veenendaal, the Netherlands). All patients were given 4 daily consecutive sessions of intrarectal HDR brachytherapy before surgery, which was done 6–8 weeks later.
Follow-up	**Median 55 months**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues:
Tumours were staged preoperatively by endorectal ultrasound and MRI.

Study population issues:
34% of patients were N+ by preoperative staging.

Other issues:
The chemotherapy regimen used by the centre was changed in 2006 and external beam radiation was no longer given in the adjuvant setting.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **285** Histopathology of surgical specimens: • ypT0 (complete pathological response, tumour regression grade [TRG]1)=27% • microfoci of residual disease (TRG2)=37% • gross residual tumour(TRG3)=36% • lymph node positive=29% All but 2 patients had negative circumferential resection margins. Actuarial local recurrence rate at 5 years=5% (local recurrence was defined as any tumour bed recurrence or pelvic node recurrence any time during the follow-up either as the first event or after the development of systemic metastases). Nine of 12 patients had a tumour bed recurrence alone or with nodal or systemic metastases; 3 patients had intra-mesocolon nodes involved with their primary recurrences and 5 other patients had inguinal or iliac nodes recurrence with retroperitoneal or distant metastases. Six of the 12 patients with pelvic recurrences received postoperative adjuvant radiation with chemotherapy based on positive nodes in the pathological specimen. Disease-free survival=65% Overall survival rate=68%	• Acute grade 1-2 proctitis was observed in all patients 7–10 days after the treatment • Grade 3 acute proctitis=1% (2 patients needed a blood transfusion because of bleeding from the clips) • Small bowel enteritis=1.4% (4/285) (all 4 patients had postoperative external beam radiation and chemotherapy) • Second cancer=2.1% (6/285) (after a median follow-up of 60 months) No pelvic fractures were observed. Complications after total mesorectal excision surgery: • Clinical anastomosis=10% • Perineal wound infection=12%
Abbreviations used: TRG, tumour regression grade	

Study 7 Sun Myint A (2010)

Details

Study type	**Case series**
Country	UK
Recruitment period	2004 onwards
Study population and number	**n=34** Patients with locally advanced rectal cancer (cT2: 5; cT3: 23; cT4: 6; cN0: 2; cN1: 21; N2: 11)
Age and sex	Median 67 years (range 39–81) 71% (24/34) male
Patient selection criteria	All patients had colonoscopy and biopsy with confirmation of the diagnosis by histological examination. All patients had a pelvic MRI and a CT scan of the chest, abdomen and pelvis. All patients had locally advanced disease either bulky low T2 (<6 cm from the anal verge) or T3 with a threatened circumferential resection margin or multiple suspicious lymph nodes. Patients with metastatic and advanced stage (circumferential and clinically fixed tumours) were excluded from the radical treatment group.
Technique	Treatment was initiated using external beam radiotherapy or chemoradiotherapy 45 Gy/25 fractions over 5 weeks. For those patients who were fit for surgery , if there was a good response (>80% regression), an HDR brachytherapy boost of 10 Gy at 10 mm from the surface of the applicator was given followed by surgery 6–8 weeks later. An OncoSmart® applicator, which is flexible, was used in 74% (25/34) of patients. A single line source was used in 7 patients and a postoperative vaginal type applicator was used in 2 patients.
Follow-up	**Median 17 months (range 5–41)**
Conflict of interest/source of funding	The first author is an advisor on Nucletron rectal brachytherapy coalition board and is a specialist advisor for NICE.

Analysis

Follow-up issues:
Patients were followed up at 3-monthly intervals during the first 2 years and 6-monthly thereafter up to 5 years. CT scans were done at 12, 24 and 36 months in addition to physical examination and rectoscopy at each visit. Colonoscopy was done initially and 3–5 yearly. Patients who were not fit for surgery or who refused surgery were also followed up regularly.

Study design issues:
Of the 34 patients, 1 had radiotherapy alone and the rest had chemoradiotherapy before surgery.

Before the brachytherapy boost, tumour response was assessed by MRI scan and endoscopy at 4 weeks.

The brachytherapy applicator had 8 treatment channels: 5 channels were used in 19 patients, 6 channels in 5 patients and all 8 channels in 1 patient. This meant the rectal mucosa that was not involved in the tumour was spared in the majority of cases.

All patients were intended to have surgery but 2 refused, 1 developed distant metastases, 1 was found to have an unresectable tumour, and 1 was unfit for major surgery.

Study population issues:
All patients had a good performance status being either PS 0 or 1.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **34** **Response to treatment (Clinical and radiological response before surgery)** • Good (>80% regression of tumour bulk endoscopically)=35% (12/34) • Moderate (50–80% regression)=44% (15/34) • Poor (<50% regression)=21% (7/34) **Pathological response** • Pathological complete remission (TRG 1)=31% (9/29) • A few scattered residual tumour cells with abundant fibrosis (TRG 2)=41% (12/29) • A few residual cells and little fibrosis (TRG 3)=14% (4/29) • Many tumour cells and little fibrosis (TRG 4)=14% (4/29) Of the 29 patients who had surgery, 80% (n=24) had an R0 resection. **Recurrence and survival (median follow-up=17 months, n=32)** • Local recurrence=0 • Distant metastases=11 • Death caused by rectal cancer=6 • Death caused by all causes=10 Progression-free survival at 1 year=79% Progression-free survival at 2 years=66% Overall survival at 1 year=90% Overall survival at 2 years=72%	• Delayed wound healing=6.9% (2/29) (Both patients had an abdominoperineal excision and the perineal wound healed by secondary intention) • Anastomotic leakage=6.9% (2/29) (Both responded to conservative treatment) • Small bowel intestinal obstruction=3.5% (1/29) (patient needed a second laparotomy within 10 days. This was not thought to be directly related to the brachytherapy boost.) • Stricture=3.5% (1/29) (successfully treated by balloon dilatation) • Mild bleeding=3.5% (1/29) (responded to conservative treatment) 2 patients died during the postoperative period because of myocardial infarction not thought to be related to HDR brachytherapy. Both patients had a history of ischaemic heart disease with previous myocardial infarctions.
Abbreviations used: TRG, tumour regression grade	

Study 8 Yanagi H (1997) (included in previous overview)

Details

<table>
<tr><td>Study type</td><td>Non-randomised controlled study (retrospective)</td></tr>
<tr><td>Country</td><td>Japan</td></tr>
<tr><td>Recruitment period</td><td>1986–95</td></tr>
<tr><td>Study population and number</td><td>n=230 (96 preoperative moderate dose intraluminal brachytherapy [IBT] and radical surgery, 19 preoperative high dose IBT and radical surgery, 115 surgery alone)
Patients with rectal cancer in the middle or lower rectum.
<table>
<tr><th>Dukes' stage</th><th>IBT group (moderate dose)</th><th>IBT group (high dose)</th><th>Control group</th></tr>
<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>
</table>
*p=0.009</td></tr>
<tr><td>Age and sex</td><td>Median age (years):
Moderate dose IBT = 59 (range 25–87)
High dose IBT = 65 (range 46–86)
Control group = 59 (range 30–83)</td></tr>
<tr><td>Patient selection criteria</td><td>Middle or lower rectal cancer, of variable Dukes' stage.</td></tr>
<tr><td>Technique</td><td>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.</td></tr>
<tr><td>Follow-up</td><td>Median follow-up (months):
Moderate dose IBT = 49.5 (range 8.6–60)
High dose IBT = 60 (range 6–60)
Control group = 47.5 (range 9.2–60)</td></tr>
<tr><td>Conflict of interest/source of funding</td><td>Not reported</td></tr>
</table>

Analysis

Study design issues:
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 by it.

Moderate dose IBT was defined as 16–40 Gy and high dose as 40–80 Gy. 'Moderate' and 'high' dose relates to the total dose of radiation rather than the dose rate.

Study population issues:
There were statistically significant differences in the preoperative tumour stage between treated cases and controls in terms of Dukes' classification and histological differentiation.

Other issues:
Although the paper does not state that this is high dose rate brachytherapy, it is cited as being so by Vuong et al.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 230 (96 vs 19 vs 115)
Sphincter-saving resection
• High dose IBT=63% (12/19)
• Moderate dose IBT=72% (69/96)
• Controls=42% (48/115)
p<0.0001 (moderate dose versus controls)

Lymph node metastases localised in perirectal tissue (Dukes' C patients)
• High dose IBT=40% (2/5)
• Moderate dose IBT=73% (30/41)
• Controls=34% (15/44)
p=0.02

Local recurrence
• High dose IBT=5% (1/19)
• Moderate dose IBT=8% (8/96)
• Controls=21% (24/115)
p=0.005

Distant recurrence
• High dose IBT=16% (3/19)
• Moderate dose IBT=23% (22/96)
• Controls=17% (19/115)

Disease-free survival
• High dose IBT=68% (13/19)
• Moderate dose IBT=72% (69/96)
• Controls=65% (75/115)

Actuarial probability of local recurrence at 5 years (Kaplan–Meier)
• High dose IBT (actual recurrence)=6%
• Moderate dose IBT=11%
• Controls=26%

Actuarial probability of survival rate for 5 years (Kaplan–Meier)
• High dose IBT=63%
• Moderate dose IBT=62%
• Controls=65%

Actuarial probability of survival rate for 5 years (Kaplan–Meier) by Dukes' stage
<table>
<tr><td></td><td>A</td><td>B</td><td>C</td><td>D</td></tr>
<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>
</table>
</td><td>
IBT-related complications (such as radiation ileitis and proctitis)
• High dose IBT=74% (14/19)
• Moderate dose IBT=38% (36/96)

Surgical interventions for complications were needed in 37% (7/19) patients in high dose group and 7% (7/96) patients in moderate dose group.

16% (3/19) patients in high dose group were converted to permanent stoma after initial sphincter sparing resection because of complications.

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.
</td></tr>
<tr><td colspan="2">Abbreviations used: HDR, high dose rate; IBT, intraluminal brachytherapy therapy</td></tr>
</table>

Study 9 Kusunoki M (1997) (included in previous overview)

Details

<table>
<tr><td>Study type</td><td>Case series</td></tr>
<tr><td>Country</td><td>Japan</td></tr>
<tr><td>Recruitment period</td><td>1986–95</td></tr>
<tr><td>Study population and number</td><td>n=106 (87 moderate dose intraluminal brachytherapy, 19 high dose)
Patients with rectal cancer.
<table>
<tr><th>Dukes' stage</th><th>IBT group (moderate dose)</th><th>IBT group (high dose)</th></tr>
<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>
</table></td></tr>
<tr><td>Age and sex</td><td>Median age (years):
Moderate dose IBT=59 (range 25–87)
High dose IBT=65 (range 46–86)</td></tr>
<tr><td>Patient selection criteria</td><td>Not reported</td></tr>
<tr><td>Technique</td><td>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.</td></tr>
<tr><td>Follow-up</td><td>0.5–9 years</td></tr>
<tr><td>Conflict of interest/source of funding</td><td>Not reported</td></tr>
</table>

Analysis

Study design issues:
Consecutive recruitment of patients.

'Moderate' and 'high' dose relates to the total dose of radiation rather than the dose rate.

Study population issues:
Same study centre as Yanagi et al.

Other issues:
Although the paper does not state that this is high dose rate brachytherapy, it is cited as being so by Vuong et al.

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).

From the absence of Dukes' stage D patients it can be assumed that treatment intent was curative, although this is not explicitly stated.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **106** **Sphincter saving resection** • High dose IBT=63% (12/19) • Moderate dose IBT=74% (64/87) The paper states that IBT did not affect the surgical procedure or the postoperative course of patients who underwent restorative surgery.	Complications requiring treatment **Fistula formation** • High dose=16% (3/19) • Moderate dose=5% (4/87) **Anastomotic dehiscence** • High dose=0% (0/19) • Moderate dose=5% (4/87) **Pelvic sepsis** • High dose=11% (2/19) • Moderate dose=2% (2/87) **Wound sepsis** • High dose=5% (1/19) • Moderate dose=3% (3/87) **Small bowel perforation** • High dose=11% (2/19) • Moderate dose=0% (0/87) **Small bowel obstruction** • High dose=11% (2/19) • Moderate dose=7% (6/87) (All were successfully treated without surgery) **Colonic pouch complication** • High dose=5% (1/19) • Moderate dose=6% (5/87) **Perianal skin complication** • High dose=32% (6/19) • Moderate dose=17% (15/87) **Anastomotic stricture** • High dose=0% (0/19) • Moderate dose=3% (3/87) **Radiation colitis** • High dose=0% (0/19) • Moderate dose=1% (1/87) **Stoma complication** • High dose=0% (0/19) • Moderate dose=1% (1/87) **Cerebral infarction** • High dose=5% (1/19) • Moderate dose=0% (0/87) 12 patients required surgical intervention for complications.
Abbreviations used: IBT, intraluminal brachytherapy	

Study 10 Yau I (2009)

Details

Study type	**Non-randomised comparative series**
Country	Canada
Recruitment period	2005 onwards
Study population and number	**n=89 (38 high dose rate brachytherapy, 51 external beam radiotherapy)** Men with advanced rectal cancer
Age and sex	Age range: 32–87 years
Patient selection criteria	Normal hormone levels before treatment.
Technique	High dose rate brachytherapy: 26 Gy was given over 4 daily treatments (6.5 Gy daily) using a remote afterloading delivery system followed by surgery 6–8 weeks later. External beam radiotherapy: 45.0–50.4 Gy in 1.8 Gy per daily fraction, 5 days per week over 5–5.5 weeks. Radiation was given with concurrent chemotherapy.
Follow-up	**17 months**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues:
An additional 30 patients with initially abnormal hormone profiles were excluded from the study.

Hormone levels were measured at baseline, at completion of radiotherapy and during routine follow-up visits every 3 months during the first 2 years and every 6 months until the 5-year mark.

Study population issues:
Same study centre as Vuong et al. and there is likely to be patient overlap.

The majority of patients in both groups had tumours located in the lower and middle third distances from the anal verge. All upper third lesions were treated by external beam radiotherapy.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **89 (38 versus 51)**

Mean serum hormone levels before and after treatment (based on periodic blood tests taken during each follow-up visit) based on tumour location

	High dose rate brachytherapy		External beam radiotherapy		p value
	Before treatment (SD)	After treatment (SD)	Before treatment (SD)	After treatment (SD)	
FSH IU/L (lower)	6.58 (3.1)	17.20 (7.9)	6.38 (2.4)	22.14 (8.6)	0.06
FSH IU/L (middle)	6.59 (3.1)	17.03 (9.0)	5.34 (2.7)	16.38 (6.7)	0.83
LH IU/L (lower)	5.39 (2.18)	7.47 (3.1)	5.17 (1.9)	9.78 (4.3)	0.06
LH IU/L (middle)	4.67 (2.0)	5.14 (2.0)	4.64 (1.9)	6.76 (2.6)	0.10
Testosterone nmol/l (lower)	16.02 (4.7)	14.49 (4.7)	15.12 (4.6)	13.05 (4.9)	0.35
Testosterone nmol/l (middle)	14.38 (3.6)	12.45 (4.0)	12.97 (4.7)	11.6 (3.9)	0.61

The following reference ranges were used for comparison:
FSH=1.2–18.5 IU/L; LH=2.5–16.3 IU/L; testosterone=10.0–38.5 nmol/L

Testosterone to LH ratio (used to evaluate Leydig cell damage) for lower third tumours (estimated from graphical presentation):

- High dose rate brachytherapy=2.75 nmol/unit
- External beam radiotherapy=1.75 nmol/unit, p=0.0036

Testosterone to LH ratio for middle third tumours (estimated from graphical presentation):

- High dose rate brachytherapy=2.85 nmol/unit
- External beam radiotherapy=1.9 nmol/unit, p=0.58

2-year hypogonadism rate (based on the International Society for the Study of the Aging Male definition) for patients with lower or middle third tumours:

- High dose rate brachytherapy=2.6%
- External beam radiotherapy=17.6%, p=0.09

Safety

Abbreviations used: FSH, follicle stimulating hormone; LH, luteinising hormone; SD, standard deviation

Efficacy

Sphincter preservation surgery

A non-randomised comparative trial of 230 patients treated by preoperative intraluminal brachytherapy and surgery or surgery alone reported that 72% (69/96) of patients treated by brachytherapy had sphincter preserving resection, compared against 42% (48/115) of controls ($p<0.0001$)[8]. A case series of 106 patients reported that 72% (76/106) of patients had sphincter sparing surgery[9]. A non-randomised comparative trial of 36 patients treated by preoperative intraluminal brachytherapy or preoperative external beam radiotherapy (EBRT) reported that 71% (12/17) of patients treated by brachytherapy had sphincter preserving resection, compared against 58% (11/19) of controls ($p=0.04$)[3]. A randomised controlled trial of 221 patients treated by preoperative high dose rate (HDR) brachytherapy or standard chemoradiation therapy reported no difference in the prevalence of stoma between the groups (66% in 2-year survivors and 65% in 5-year survivors in the brachytherapy group)[2].

Resection margins

The randomised controlled trial of 243 patients treated by preoperative HDR brachytherapy or standard chemoradiation therapy reported R0 resection in 99% (87/90) and 90% (83/92) of patients respectively ($p=0.03$)[1]. A non-randomised comparative trial of 954 patients treated by preoperative HDR brachytherapy, short course radiotherapy or surgery alone reported R0 resection in 97% (307/318), 83% (265/318) and 74% (236/318) of patients respectively ($p=0.5$ for brachytherapy versus short course radiotherapy)[5].

Histopathology of surgical specimens

The randomised controlled trial of 243 patients treated by preoperative HDR brachytherapy or standard chemoradiation therapy reported a major response (tumour regression grade 1 and 2) in 44% (35/80) and 28% (23/82) of patients respectively ($p=0.04$)[1]. The difference in response rate was greater for tumours less than 3.7 cm in diameter. The non-randomised comparative trial of 36 patients treated by preoperative intraluminal brachytherapy or preoperative EBRT reported that 59% (10/17) of patients treated by brachytherapy had a complete pathological response (ypT0), compared against 16% (3/19) of controls ($p=0.0001$)[3]. A case series of 285 patients reported a complete pathological response rate of 27%[6]. A case series of 34 patients reported a complete pathological response rate of 31% (9/29)[7].

Local recurrence

The non-randomised comparative trial of 230 patients reported that 8% (8/96) of patients treated by intraluminal brachytherapy developed local recurrence, compared against 21% (24/115) of patients treated by surgery alone ($p=0.005$)[8]. The case series of 285 patients reported an actuarial local recurrence rate at 5 years of 5%[5]. A case series of 34 patients reported no local recurrence after a median follow-up of 17 months[7].

Progression-free or disease-free survival

The randomised controlled trial of 221 patients treated by preoperative HDR brachytherapy or standard chemoradiation therapy reported progression-free 5-year survival of 52% and 64%, respectively (p=0.32)[2]. The case series of 34 patients reported progression-free survival of 66% at 2 years[7]. The non-randomised comparative trial of 230 patients reported disease-free survival at follow-up for 72% (69/96) patients treated by brachytherapy (median follow-up 49.5 months) compared against 65% (75/115) for controls treated by surgery alone (median follow-up 47.5 months; p value not stated)[8]. The case series of 285 patients reported 5-year disease-free survival of 65%[6].

Overall survival

The randomised controlled trial of 221 patients treated by preoperative HDR brachytherapy or standard chemoradiation therapy reported overall 5-year survival of 64% and 71%, respectively (p=0.34)[2]. The non-randomised comparative trial of 230 patients reported actuarial probability of 5-year survival of 62% for patients treated by brachytherapy and 65% for controls treated by surgery alone[8]. The case series of 285 patients reported 5-year overall survival of 68%[6]. The case series of 34 patients reported overall survival of 72% at 2 years[7].

Safety

Acute toxicity

A randomised controlled trial of 243 patients reported the following grade 2 toxicity events in patients treated by HDR brachytherapy: neutropaenia (1%), nausea (6%), vomiting (2%), stomatitis (2%), diarrhoea (19%), 'skin' (20%), dysuria (6%) and proctitis (18%)[1]. Similar rates were seen in patients treated by standard chemoradiotherapy. A non-randomised comparative trial of 230 patients reported that 74% (14/19) of patients treated by a high total dose and 38% (36/96) of patients treated by a moderate total dose had brachytherapy-related complications such as radiation ileitis and perianal skin problems[8]. Grade 3 acute proctitis was reported in 1% (2/285) of patients in a case series of 285 patients. Rectal pain was reported in 71% (12/17) of patients treated by HDR brachytherapy in a non-randomised comparative study[3].

Rectal perforation

Rectal perforation during surgery was reported in 4% (13/318) of patients treated by HDR brachytherapy in a non-randomised comparative trial of 954 patients[5]. Small bowel perforation was reported in 2% (2/106) of patients in a case series of 106 patients[9].

Mortality

Death within 30 days of surgery was reported in 1% (3/318) of patients treated by HDR rate brachytherapy in the non-randomised comparative trial of 954 patients[5]. Death during the postoperative period, from cardiac complications, was reported in 1 patient treated by preoperative HDR brachytherapy in the randomised controlled trial of 243 patients[1].

Infection

Infection related to the wound was reported in 15% (16/106) of patients treated by preoperative HDR brachytherapy in the randomised controlled trial of 243 patients[1]. Infection was reported in 9% (30/318) of patients treated by HDR brachytherapy in the non-randomised comparative trial of 954 patients; wound infection was also reported in 9% (29/318) of patients[5]. In the same trial, intra-abdominal infection was reported in 11% (12/106) of patients. Pelvic sepsis and wound sepsis were each reported in 4% (4/106) of patients in the case series of 106 patients[9].

Wound dehiscence

Wound dehiscence was reported in 3% (9/318) of patients treated by HDR brachytherapy in the non-randomised comparative trial of 954 patients[5].

Anastomotic dehiscence

Anastomotic dehiscence was reported in 4% (13/318) of patients treated by HDR brachytherapy in the non-randomised comparative trial of 954 patients[5] and in 4% (4/106) of patients in the case series of 106 patients[9].

Fistula

Fistula was reported in 1 patient treated by preoperative HDR brachytherapy in the randomised controlled trial of 243 patients[1]. Fistula was reported in 7% (7/106) of patients in the case series of 106 patients[9].

Stricture

Stricture was reported in 1 patient in a case series of 34 patients[7]. Anastomotic stricture was reported in 3% (3/106) of patients in the case series of 106 patients[9].

Small bowel obstruction

Small bowel obstruction was reported in 8% (8/106) of patients in the case series of 106 patients; all were successfully treated without surgery [9].

Urinary problems

Urinary problems were reported in 3% (3/106) of patients treated by preoperative HDR brachytherapy in the randomised controlled trial of 243 patients[1].

Cardiovascular complications

Cardiovascular complications within 30 days of surgery were reported in 9% (30/318) of patients treated by HDR brachytherapy in the non-randomised comparative trial of 954 patients[5].

Hand-foot syndrome

Hand-foot syndrome was reported in 1 patient treated by HDR brachytherapy in the non-randomised comparative trial of 36 patients[3].

Reoperation

Reoperation was reported in 5% (5/106) of patients treated by preoperative HDR brachytherapy compared against 8% (9/109) of patients treated by standard chemoradiotherapy in the randomised controlled trial of 243 patients[1]. Reoperation rates of 4% (13/318), 14% (45/318) and 12% (39/318) were reported for patients treated by preoperative HDR brachytherapy, short course radiotherapy, and surgery alone, respectively (p=0.0005)[5] in the non-randomised comparative trial of 954 patients. Surgical intervention for complications was reported in 11% (12/106) of patients in the case series of 106 patients[9].

Other

Cerebral infarction, stoma complication and radiation colitis were each reported in 1 patient in the case series of 106 patients[9].

Validity and generalisability of the studies

- There is 1 small case series from the UK[7].
- The patient population of 1 non-randomised comparative trial from Pakistan had a median age of 35 years, which is much younger than the other trials[3].
- The first 2 trials describe outcomes of the same trial after different periods of follow-up[1,2].
- In 1 non-randomised comparative trial, 55% of the patients in the control group were treated during the 8-year period preceding the advent of brachytherapy in that centre [8]. 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.
- One non-randomised comparative trial 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[8].
- One non-randomised comparative trial matched patients with those who were treated in a different country. There may differences in registration, surgical strategies and definition of complications between the countries. It is also possible that there may be selection bias, where patients with significant heart conditions did not receive preoperative radiotherapy[5].
- There is likely to be some patient overlap between the studies.
- Delivery systems and total brachytherapy dose varied between studies.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

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

Interventional procedures

- Preoperative high dose rate brachytherapy for rectal cancer. NICE interventional procedure guidance 201 (2006). This guidance is currently under review and is expected to be updated in 2015. For more information, see http://www.nice.org.uk/guidance/IPG201

Technology appraisals

- Laparoscopic surgery for colorectal cancer. NICE technology appraisal 105 (2006). Available from http://www.nice.org.uk/guidance/TA105

Clinical guidelines

- Colorectal cancer: The diagnosis and management of colorectal cancer. NICE clinical guideline 131 (2014). Available from http://www.nice.org.uk/guidance/CG131

Cancer Service Guidance

- Improving outcomes in colorectal cancers: Manual update (June 2004). Available from http://www.nice.org.uk/guidance/CSGCC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to where comments are considered voluminous, or publication would be unlawful or inappropriate. Three Specialist Advisor Questionnaires for preoperative high dose rate brachytherapy for rectal cancer were submitted and can be found on the NICE website [INSERT HYPER LINK TO MAIN IP PAGE].

Patient commentators' opinions

NICE's Public Involvement Programme sent 47 questionnaires to 1 NHS trust for distribution to patients who had the procedure (or their carers). NICE received 18 completed questionnaires.

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

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.
- This overview does not include patients with anal cancer. Most of the literature identified reported outcomes separately for anal cancer.

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1. Jakobsen A, Ploen J, Vuong T et al. (2012) Dose-effect relationship in chemoradiotherapy for locally advanced rectal cancer: a randomized trial comparing two radiation doses. International Journal of Radiation Oncology, Biology, Physics 84: 949-954
2. Appelt AL, Vogelius IR, Ploen J et al. (2014) Long-term results of a randomized trial in locally advanced rectal cancer: no benefit from adding a brachytherapy boost. International Journal of Radiation Oncology, Biology, Physics 90: 110–8
3. Tunio MA, Rafi M, Hashmi A et al. (2010) High-dose-rate intraluminal brachytherapy during preoperative chemoradiation for locally advanced rectal cancers. World Journal of Gastroenterology 16: 4436-4442
4. Smith JA, Wild AT, Singhi A et al. (2012) Clinicopathologic comparison of high-dose-rate endorectal brachytherapy versus conventional chemoradiotherapy in the neoadjuvant setting for resectable stages II and III low rectal cancer. International Journal of Surgical Oncology: Article ID406568
5. Hesselager C, Vuong T, Pahlman L et al. (2013) Short-term outcome after neoadjuvant high-dose-rate endorectal brachytherapy or short-course external beam radiotherapy in resectable rectal cancer. Colorectal disease 15: 662–6
6. Vuong T, Richard C, Niazi T et al. (2010) High dose rate endorectal brachytherapy for patients with curable rectal cancer. Seminars in Colon and Rectal Surgery 21: 115–9
7. Sun Myint A, Mukhopadhyay T, Ramani VS et al. (2010) Can increasing the dose of radiation by HDR brachytherapy boost following pre operative chemoradiotherapy for advanced rectal cancer improve surgical outcomes? Colorectal Disease 12: 30–6
8. 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
9. 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
10. Yau I, Vuong T, Garant A et al. (2009) Risk of hypogonadism from scatter radiation during pelvic radiation in male patients with rectal cancer. International Journal of Radiation Oncology, Biology, Physics 74: 1481–6

Appendix A: Additional papers on preoperative high dose rate brachytherapy for rectal cancer

The following table outlines the studies that are considered potentially relevant to the IP 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	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Appelt AL, Ploen J, Vogelius I et al. (2013) Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. International Journal of Radiation Oncology, Biology, Physics 85: 74-80	n=222	This study demonstrated a significant dose-response relationship for tumor regression after preoperative CRT for locally advanced rectal cancer for tumor dose levels in the range of 50.4-70 Gy, which is higher than the dose range usually considered.	The study uses data from 2 previously published studies (Jakobsen et al, 2012 and Jakobsen et al, 2006)
Appelt AL, Bentzen SM, Jakobsen A et al. (2014) Dose-response of acute urinary toxicity of long-course preoperative chemoradiotherapy for rectal cancer. Acta Oncol 1-8	n=345	The predicted risk of grade 2 and above cystitis ranged from 2% to 26%. Acute cystitis correlated significantly with radiation dose to the bladder. Male gender and brachytherapy boost increased the risk of toxicity.	The study reported a dose-response model for acute urinary toxicity. A study from the same centre is included (Jakobsen A, 2012).
El-Sayed ME, El-Taher ZH (2008) Prospective phase II study of brachytherapy boost as a component of neo-adjuvant chemotherapy and external beam radiation therapy in locally advanced rectal cancer. Journal of Egyptian National Cancer Institute 20: 10-16	n=17	The use of high dose rate brachytherapy as a boost in the neoadjuvant chemotherapy and radiation therapy setting in locally advanced rectal cancer is an acceptable modality with an appreciable clinical and pathological response rates as well as an acceptable toxicity profile	Larger studies are included.
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	n=41	Recurrence = 27% (11/41) Local recurrence = 15% (6/41) Cancer-related deaths = 15% (6/41) Cumulative 5-year survival rate (Kaplan–Meier) = 82.9% Cumulative 5-year disease-free survival rate (Kaplan–Meier) = 71.8%	Larger or more recent studies are included. Included in previous overview.
Jakobsen A, Mortensen JP, Bisgaard C et al. (2008) A COX-2 inhibitor combined with chemoradiation of locally advanced rectal cancer: A phase II trial. International Journal of Colorectal Disease 23: 251–5	n=35	The addition of a COX-2 inhibitor to chemotherapy-enhanced radiation treatment of rectal cancer was not feasible due to a high incidence of rash in the present study.	Small case series investigating the possible effect of a COX-2 inhibitor in addition to chemoradiation.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
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	n=50	No residual tumour=27% (13/48) Microscopic tumour only=27% (13/48) Moderate tumour response=40% (19/48) Minor response=8% (4/48) Wound infection=6% (3/48) Postoperative ileus=4% (2/48) Anastomotic leakage=0% (0/48) Reoperation=8% (4/48)	Larger or more recent studies are included. Included in previous overview.
Kuehne J, Kleisli T, Biernacki P et al.(2003) Use of high-dose-rate brachytherapy in the management of locally recurrent rectal cancer. Diseases of the Colon and Rectum 46: 895–9	n=27 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, Yanagi H, Kamikonya N et al. (1996) Significant effects of preoperative intraluminal brachytherapy on the survival rate after resection of rectal carcinoma. International Journal of Oncology 9: 645–51	n=85	Preoperative IBT affected tumour morphology and prognosis. Proportion of residual viable cells was significantly correlated to survival.	Studies from the same centre are included.
Kusunoki M, Shoji Y, Yanagi H et al. (1993) Anorectal function after preoperative intraluminal brachytherapy and colonic J pouch-anal anastomosis for rectal carcinoma. British Journal of Surgery 80: 933–5	n=24 (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.	Studies from the same centre are included.
Neron S, Perez S, Benc R et al. (2014) The experience of pain and anxiety in rectal cancer patients during high-dose-rate brachytherapy. Current Oncology 21: e89-e95	n=25	Most patients with rectal cancer tolerated high dose rate rectal brachytherapy well, although the procedure is stressful and painful for some.	Small case series.
Poon E, Williamson JF, Vuong T et al. (2008) Patient-specific Monte Carlo dose calculations for high-dose-rate endorectal brachytherapy with shielded intracavitary applicator. International Journal of Radiation Oncology, Biology, Physics 72: 1259-1266	n=43	The shielded applicator improved dose conformity and normal tissue sparing; however, Task Group 43-based treatment planning might compromise target coverage by not accounting for shielding.	Small case series focusing on dose calculations with shielded applicator.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
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. Radiotherapy and Oncology 76 (Suppl. 2): S137–S138	n=5	Flexible applicator allows better treatment geometry and the possibility of treating tumours situated higher in the rectum.	No safety or efficacy data are presented.
Vuong T, Niazi T, Artho G et al. (2010) Local pelvic relapses after neoadjuvant high-dose rate endorectal brachytherapy for patients with operable rectal cancer. Current Colorectal Cancer Reports 6: 228-234	n=325	At 5 years, the actuarial local recurrence rate is 4.7%, disease-free survival is 68%, and overall survival is 71%.	A paper with more detailed patient outcomes from the same centre is included.
Vuong T, Devic S, Podgorsak E (2007) High dose rate endorectal brachytherapy as a neoadjuvant treatment for patients with resectable rectal cancer. Clinical Oncology (Royal College of Radiologists) 19: 701-705	n=100 Median follow-up=60 months	At a median follow-up time of 60 months, the 5-year actual local recurrence rate was 5%, disease-free survival was 65%, and overall survival was 70%. High dose rate endorectal brachytherapy seems to prevent local recurrence and has a favourable toxicity pattern compared with external beam radiotherapy.	A larger, more recent study from the same centre is included.
Vuong T, Devic S, Moftah B et al. (2005) High-dose-rate endorectal brachytherapy in the treatment of locally advanced rectal carcinoma: technical aspects. Brachytherapy 4: 230–5	n=49	The pathology specimens showed a complete macroscopic response in 64% of the patients and tumor downstaging in 67% of the patients. The use of a multichannel flexible endorectal applicator leads to tumor downstaging before surgery in patients with resectable locally advanced rectal carcinomas.	A more recent study from the same centre is included. Included in previous overview.
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	n=49	A complete clinical response was obtained in 32 of 47 (68%) patients with 32% pathologically pT0N0-1, and 36% had only residual microfoci of carcinoma. The surgical approaches did not yield more complications than expected.	A more recent study from the same centre is included. Included in previous overview.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Yanagi H, Kusunoki M, Kamikonya N (1992) Small-bowel perforation after preoperative high-dose-rate intraluminal brachytherapy for rectal carcinoma. AJR: American Journal of Roentgenology 159: 224	n=2	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. Surgery Today 30: 410–15	n=230 (115 treated with IBT and 115 historical controls).	Good local control achieved for T3 stage with IBT, similar to T ≤ 2 in both groups.	Studies from the same centre are included. Results compare N+ and N– patients.
Zlobec I, Vuong T, Hayashi S et al. (2007) A simple and reproducible scoring system for EGFR in colorectal cancer: application to prognosis and prediction of response to preoperative brachytherapy. British Journal of Cancer 96: 793-800	n=82	Epidermal growth factor receptor is a predictive marker of response to preoperative radiotherapy.	Study focuses on the predictive and prognostic value of epidermal growth factor receptor (EGFR) expression.
Zlobec I, Vuong T, Compton CC (2006) The predictive value of apoptosis protease-activating factor 1 in rectal tumors treated with preoperative, high-dose-rate brachytherapy. Cancer 106: 284-286	n=94	30 tumours had complete pathologic tumour regression after preoperative radiotherapy. Of these, 18 tumours were positive for APAF-1. A partial response occurred in 35 tumours. 18 tumours (51%) were positive for the protein. Only 8 of 29 nonresponsive tumors (28%) were immunoreactive for APAF-1.	Study focuses on the predictive value of apoptosis protease-activating factor 1.

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

Guidance	Recommendations
Interventional procedures	**Preoperative high dose rate brachytherapy for rectal cancer. NICE interventional procedure guidance 201 (2006) [current guidance]** 1.1 Current evidence on the short-term safety of preoperative high dose rate brachytherapy for rectal cancer and its efficacy in reducing tumour bulk appears adequate. However, evidence about the advantages of the procedure as an adjunct to surgery and its effect on long-term survival is not adequate to support the use of this procedure without special arrangements for consent, audit and clinical governance. 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 Trusts. • Inform patients, as part of the consent process, about the uncertainty of the procedure influencing their long-term survival, and provide them with clear written information. Use of the Institute's information for patients ('Understanding NICE guidance') is recommended. • Audit and review clinical outcomes of all patients having preoperative high dose rate brachytherapy for rectal cancer (see section 3.1). 1.3 Further research will be useful, and clinicians are encouraged to enter patients into well-designed trials and to collect longer-term follow-up data. The Institute may review the procedure upon publication of further evidence.
Technology appraisals	**Laparoscopic surgery for colorectal cancer. NICE technology appraisal 105 (2006).** 1.1 Laparoscopic (including laparoscopically assisted) resection is recommended as an alternative to open resection for individuals with colorectal cancer in whom both laparoscopic and open surgery are considered suitable. 1.2 Laparoscopic colorectal surgery should be performed only by surgeons who have completed appropriate training in the technique and who perform this procedure often enough to maintain competence. The exact criteria to be used should be determined by the relevant national professional bodies. Cancer networks and constituent Trusts should ensure that any local laparoscopic colorectal surgical practice meets these criteria as part of their clinical governance arrangements. 1.3 The decision about which of the procedures (open or laparoscopic)

<table>
<tr><td></td><td>is undertaken should be made after informed discussion between the patient and the surgeon. In particular, they should consider:
• the suitability of the lesion for laparoscopic resection
• the risks and benefits of the two procedures
• the experience of the surgeon in both procedures.</td></tr>
<tr><td>Clinical guidelines</td><td>Colorectal cancer: The diagnosis and management of colorectal cancer. NICE clinical guideline 131 (2014).

1.2 Management of local disease

1.2.1 Preoperative management of the primary tumour

For the purposes of this guideline we have defined 3 different risk groups of patients with rectal cancer, according to the risk of local recurrence. These groups are defined in table 1.
Table 1 Risk of local recurrence for rectal tumours as predicted by MRI
<table>
<tr><th>Risk of local recurrence</th><th>Characteristics of rectal tumours predicted by MRI</th></tr>
<tr><td>High</td><td>• A threatened (<1 mm) or breached resection margin or
• Low tumours encroaching onto the inter-sphincteric plane or with levator involvement</td></tr>
<tr><td>Moderate</td><td>• Any cT3b or greater, in which the potential surgical margin is not threatened or
• Any suspicious lymph node not threatening the surgical resection margin or
• The presence of extramural vascular invasion[a]</td></tr>
<tr><td>Low</td><td>• cT1 or cT2 or cT3a and
• No lymph node involvement</td></tr>
<tr><td colspan="2">[a] This feature is also associated with high risk of systemic recurrence.</td></tr>
</table>
Patients whose primary rectal tumour appears resectable at presentation

1.2.1.1 Discuss the risk of local recurrence, short-term and long-term morbidity and late effects with the patient after discussion in the multidisciplinary team (MDT). [2011]

1.2.1.2 Do not offer short-course preoperative radiotherapy (SCPRT) or chemoradiotherapy to patients with low-risk operable rectal cancer</td></tr>
</table>

	(see table 1 for risk groups), unless as part of a clinical trial. [2011] 1.2.1.3 Consider SCPRT then immediate surgery for patients with moderate-risk operable rectal cancer (see table 1 for risk groups). Consider preoperative chemoradiotherapy with an interval to allow tumour response and shrinkage before surgery for patients with tumours that are borderline between moderate and high risk. [2011] 1.2.1.4 Offer preoperative chemoradiotherapy with an interval before surgery to allow tumour response and shrinkage (rather than SCPRT), to patients with high-risk operable rectal cancer (see table 1 for risk groups). [2011] Patients whose primary colon or rectal tumour appears unresectable or borderline resectable 1.2.1.5 Discuss the risk of local recurrence and late toxicity with patients with rectal cancer after discussion in the MDT. [2011] 1.2.1.6 Offer preoperative chemoradiotherapy with an interval before surgery, to allow tumour response and shrinkage, to patients with high-risk locally advanced rectal cancer. [2011] 1.2.1.7 Do not offer preoperative chemoradiotherapy solely to facilitate sphincter-sparing surgery to patients with rectal cancer. [2011] 1.2.1.8 Do not routinely offer preoperative chemotherapy alone for patients with locally advanced colon or rectal cancer unless as part of a clinical trial. [2011] 1.2.2 Colonic stents in acute large bowel obstruction 1.2.2.1 If considering the use of a colonic stent in patients presenting with acute large bowel obstruction, offer CT of the chest, abdomen and pelvis to confirm the diagnosis of mechanical obstruction, and to determine whether the patient has metastatic disease or colonic perforation. [2011] 1.2.2.2 Do not use contrast enema studies as the only imaging modality in patients presenting with acute large bowel obstruction. [2011] 1.2.2.3 For patients with acute left-sided large bowel obstruction caused by colorectal cancer that is potentially curable, and for whom surgery is suitable:

	• Resuscitate patients and explain to them and their family members or carers (as appropriate) that acute bowel obstruction can initially be managed either with emergency surgery or a colonic stent, and that there is no clear evidence that one treatment is better than the other. [new 2014] • Offer patients the chance to take part in a randomised controlled trial[2] (if available) that compares emergency surgery with colonic stent insertion to initially manage acute bowel obstruction. [new 2014] 1.2.2.4 For patients with acute left-sided large bowel obstruction caused by colorectal cancer that is not potentially curable, or for whom surgery is unsuitable: [new 2014] • Resuscitate patients with acute large bowel obstruction, then consider placing a self-expanding metallic stent to initially manage a left-sided complete or near-complete colonic obstruction. [2011] • A consultant colorectal surgeon should consider inserting a colonic stent in patients presenting with acute large bowel obstruction. They should do this together with an endoscopist or a radiologist (or both) who is experienced in using colonic stents. [2011] 1.2.2.5 Do not place self-expanding metallic stents: • in low rectal lesions or • to relieve right-sided colonic obstruction or • if there is clinical or radiological evidence of colonic perforation or peritonitis. [2011] 1.2.2.6 Do not dilate the tumour before inserting the self-expanding metallic stent. [2011] 1.2.2.7 Only a healthcare professional experienced in placing colonic stents who has access to fluoroscopic equipment and trained support staff should insert colonic stents. [2011] 1.2.3 Stage I colorectal cancer 1.2.3.1 The colorectal MDT should consider further treatment for patients with locally excised, pathologically confirmed stage I cancer, taking into account pathological characteristics of the lesion, imaging results and previous treatments. [2011] 1.2.3.2 Offer further treatment to patients whose tumour had involved resection margins (less than 1 mm). [2011]

	1.2.4 Stage I rectal cancer 1.2.4.1 An early rectal cancer MDT[3] should decide which treatment to offer to patients with stage I rectal cancer, taking into account previous treatments, such as radiotherapy. [2011] 1.2.4.2 After discussion in the MDT responsible for the management of stage I rectal cancer, discuss uncertainties about the potential risks and benefits of all treatment options with patients and their family members and carers (as appropriate), taking into account each patient's circumstances. [new 2014] 1.2.4.3 Explain to patients and their family members or carers (as appropriate) that there is very little good‑quality evidence comparing treatment options for stage I rectal cancer. [new 2014] 1.2.4.4 Offer patients the chance to take part in a randomised controlled trial (if available) that compares treatment options for stage I rectal cancer. [new 2014] 1.2.5 Laparoscopic surgery – see NICE technology appraisal guidance 105 recommendations above 1.2.6 Adjuvant chemotherapy in rectal cancer 1.2.6.1 Assess pathological staging after surgery, before deciding whether to offer adjuvant chemotherapy. [2011] 1.2.6.2 Consider adjuvant chemotherapy for patients with high‑risk stage II and all stage III rectal cancer to reduce the risk of local and systemic recurrence. [2011] 1.2.8.2 The choice of adjuvant treatment should be made jointly by the individual and the clinicians responsible for treatment. The decision should be made after an informed discussion between the clinicians and the patient; this discussion should take into account contraindications and the side‑effect profile of the agent(s) and the method of administration as well as the clinical condition and preferences of the individual. [2006]
Cancer service Guidance	**Improving outcomes in colorectal cancers: Manual update (June 2004)** Although the guidance includes evidence on preoperative radiotherapy

	in the treatment of rectal cancer, it does 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

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	20/11/2014	Issue 11 of 12, November 2014
Database of Abstracts of Reviews of Effects – DARE (Cochrane)	20/11/2014	Issue 4 of 4, October 2014
HTA database (Cochrane)	20/11/2014	Issue 4 of 4, October 2014
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane)	20/11/2014	10 of 12, October 2014
MEDLINE (Ovid)	20/11/2014	1946 to November Week 1 2014
MEDLINE In-Process (Ovid)	20/11/2014	November 19, 2014
EMBASE (Ovid)	20/11/2014	1974 to 2014 Week 46
PubMed	20/11/2014	n/a
BLIC (Dialog DataStar)	20/11/2014	n/a

Trial sources searched on 19/11/2014

- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database
- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov

Websites searched on 19/11/2014

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference websites <<add details>>
- General internet search

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	(endocavit* radiotherap* or endocavit* radiation therap*).tw.
6	(implant therap* or implant radiation therap*).tw.

7	(interstitial radiotherap* or interstitial radiation therap*).tw.
8	(intraluminal radiotherap* or intraluminal radiation therap*).tw.
9	(high dose rate or high-dose rate).tw.
10	HDR.tw.
11	(endorectal adj4 (applicat* or catheter* or needle*)).tw.
12	((iodine-125 or iridium-192 or palladium-103) adj4 (seed* or pellet*)).tw.
13	oncosmart.tw.
14	papillon*.tw.
15	GammaMed.tw.
16	afterloader.tw.
17	or/1-16
18	Rectal Neoplasms/
19	Anus Neoplasms/
20	((rect* or anus or anal) adj4 (cancer* or neoplasm* or lesion* or tumour* or tumor* or malignan* or carcinoma* or adenocarcinom*)).tw.
21	or/18-20
22	17 and 21
23	Animals/ not Humans/
24	22 not 23
25	limit 24 to ed=20051130-20141130