NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of low-energy contact X-ray brachytherapy (the Papillon technique) for early-stage rectal cancer

Rectal cancer is a common form of bowel cancer that affects the rectum (the end part of the bowel). Low-energy contact X-ray brachytherapy involves placing an X-ray tube close to the cancer to shrink the tumour. Surgery may be needed if the procedure does not work well enough.

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 and updated in March 2015

Procedure name

- Low-energy contact X-ray brachytherapy (the Papillon technique) for early-stage rectal cancer

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 are treated with curative intent. It involves resection of the affected part of the rectum and the mesorectum. The anal sphincter is preserved whenever possible: a colostomy is formed when this is not possible.

In some patients, radiotherapy or chemotherapy or both are used before, during or after surgery to decrease the chances of local recurrence and metastatic disease. Radiotherapy may take the form of external-beam radiation therapy (EBRT) or radioisotope brachytherapy. EBRT uses radiation from outside the body, which is focussed on the cancer and surrounding lymph nodes. Radioisotope brachytherapy involves inserting radioactive pellets or seeds directly into the tumour (interstitial brachytherapy), or placing an endorectal treatment applicator near the tumour to deliver radiation from within the rectum (Endorectal high dose rate brachytherapy).

What the procedure involves

Low-energy contact X-ray brachytherapy (CXB; the Papillion technique) aims to improve local control or cure rectal cancer. The procedure involves inserting an X-ray tube through the anus and placing it in close contact with the tumour, to kill cancer cells and reduce the size of the tumour.

Low-energy CXB for rectal cancer is usually delivered in a day-care setting. The patient is given an enema before treatment, to clear the bowel. With the patient in a knee-to-chest, prone jack-knife or supine position, local anaesthesia and glyceryl trinitrate are applied to the anal sphincter to numb the area and relax the sphincter muscles. A sigmoidoscope is inserted to check the size and position of the tumour. A rigid endorectal treatment applicator is then inserted and placed in contact with the tumour. A contact X-ray tube is introduced into the applicator and treatment commences. The tube emits low-energy X-rays that only penetrate a few millimetres. This minimises damage to deeper tissues that are not involved in the cancer. If the tumour does not respond to low-energy CXB, or recurs after treatment, surgery may be performed.

Outcome measures

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 has penetrated the surface of the visceral peritoneum, meaning that it has grown through all layers of the colon.
- T4b: The tumour has grown into, or has attached to, other organs or structures.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to low-energy contact X-ray brachytherapy for early-stage rectal cancer. Searches were conducted of the following databases, covering the period from their commencement to 25 March 2015: 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 early-stage rectal cancer.
Intervention/test	Low-energy contact X-ray 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 1149 patients from 1 randomised controlled trial, 2 non-randomised comparative studies and 7 case series.

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 low-energy contact X-ray brachytherapy (the Papillon technique) for early-stage rectal cancer

Study 1 Ortholan C (2012)

Details

Study type	**Randomised controlled trial**
Country	France
Recruitment period	1996 to 2001
Study population and number	Patients with stage T2 or T3 rectal cancer **n=88 patients (45 low-energy CXB and EBRT versus 43 EBRT alone)**
Age and sex	CXB+EBRT group: median age, 69 years; 62% (28/45) male EBRT-alone group: median age, 67 years; 67% (29/43) male
Patient selection criteria	Inclusion criteria: Patients with histologically confirmed adenocarcinoma of the lower rectum (located within 6 cm of the anal verge), classified as a T2 or T3 by endorectal ultrasonography and involving less than two thirds of the rectal circumference were included. All patients showed no signs of distant metastases. Exclusion criteria: Not reported.
Technique	CXB was performed by delivering a 50kV photon beam with 0.5 mm aluminium filtration at a dose rate of 20 Gy per minute. A total dose of 85 Gy was delivered in 3 fractions: 35 Gy, 30 Gy and 20 Gy were delivered on days 1, 8 and 21 respectively. EBRT was performed 2 weeks after CXB commenced. The procedure was performed using a 3 field wedge technique with a total dose 39 Gy, delivered in 13 fractions over 17 days. The target volume/area included the primary rectal tumour, the perirectal nodes, the mesorectum up to the level of the lower border of the first sacral vertebra, and the lymph nodes along the internal iliac vessels. The anal verge was not irradiated, except in patients who had a tumour invading the upper part of the anus. For patients with a complete response 4 weeks after the completion of EBRT, an interstitial brachytherapy boost of 25 Gy was delivered to the tumour bed using iridium-192 implants.
Follow-up	**10 years**
Conflict of interest/source of funding	None reported

Analysis

Follow-up issues: Patients were followed-up every 3 months for the first 3 years. The regularity of follow-up appointments, after 3 years, was not described. Authors did not state whether there were any losses to follow-up.

Study design issues: Patients were allocated to groups using a block randomisation approach; no demographic stratification was performed prior to randomisation. Statistical power calculations revealed that 90 patients were needed to detect an increase in the rate of sphincter salvage from 40% to 65% (with 90% power and a 5% significance level). Some patients received a boost of interstitial brachytherapy; however, numbers were not reported. There is potential overlap with other studies included in this overview (Gerard, 1996; Gerard, 2014; and Gerard, 2002)

Study population issues: None identified

Other issues: The clinical response was determined by digital rectal examination and rigid rectoscopy.

- Complete response - no visible tumour, rectal mucosa clinically and endoscopically normal, or simple scar without suspicious induration.
- Partial 50% response – 50% reduction in the product of 2 perpendicular parameters.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **88 (45 CXB +EBRT versus 43 EBRT alone); however numbers varied by outcome measures.** **Clinical response (n=78, 42 CXB +EBRT group versus 36 EBRT alone)** • A complete clinical response was reported in 26% (11/42) of patients in the CXB+EBRT group and 33% (12/36) of patients in the EBRT-alone group at 5-week follow-up (no p value reported). • A clinical response greater than 50% was reported in 69% (29/42) of patients in the CXB+EBRT group and 67% (24/36) of patients in the EBRT-alone group at 5-week follow-up (no p value reported). • A clinical response less than 50% was reported in 5% (2/43) of patients in the CXB+EBRT group and 31% (11/36) of patients in the EBRT-alone group at 5-week follow-up (no p value reported). **Actuarial survival (Kaplan–Meier estimates)** • The overall survival rate was 55% in the CXB+EBRT group and 56% in the EBRT-alone group at 10-year follow-up (p=0.85). • The disease-free survival rate was 53% in the CXB+EBRT group and 54% in the EBRT-alone group at 10-year follow-up (p=0.99). **Disease recurrence** • The actuarial local recurrence rate (Kaplan–Meier estimate) was in 10% in the CXB+EBRT group and 15% in the EBRT-alone group at 10-year follow-up (p=0.69). • Distant recurrence was reported in 27% (12/45) in the CXB+EBRT group and 26% (11/43) in the EBRT-alone group at 10-year follow-up (no p value reported). **Sphincter saving procedures and colostomy** • All patients underwent surgery (either sphincter saving procedures or abdominoperineal resections) after initial treatment. Sphincter saving procedures were possible in 76% (34/45) of patients in the CXB+EBRT group and 44% (19/43) of patients in the EBRT-alone group (no p values reported). Abdominoperineal resections were needed in 24% (11/45) of patients in the CXB+EBRT group and 56% (24/43) of patients in EBRT-alone group (no p values reported). • The actuarial colostomy rate (Kaplan–Meier estimate) was 29% in the CXB+EBRT group and 63% in the EBRT-alone group at 10-year follow-up (p<0.001). • Colostomies were needed in 31% (14/45) of patients in the CXB+EBRT group: 24% (11/45) of patients had a colostomy due to an initial abdominoperineal resection and 7% (3/45) of patients had a late definitive colostomy. • Colostomies were needed in 63% (27/43) of patients in the EBRT-alone group: 56% (24/43) of patients had a colostomy due to an initial abdominoperineal resection and 7% (3/43) of patients had a late definitive colostomy.	• Death due to colorectal cancer was reported in 24% (11/45) of patients in the CXB+EBRT group and 28% (12/43) of patients in the EBRT-alone group at 10-year follow-up (no p value reported).
Abbreviations used: CXB, contact X-ray brachytherapy; EBRT, external beam radiotherapy	

Study 2 Gerard JP (1996)

Details

Study type	**Case series**
Country	France
Recruitment period	1977–93
Study population and number	Patients with stage T1 to T3 rectal cancer **n=101 patients treated by low-energy CXB with or without interstitial brachytherapy boost**
Age and sex	Median age, 73 years; 45.5% (46/101) male
Patient selection criteria	Inclusion criteria: patients with stage T1 to T3 infiltrating adenocarcinoma of the rectum (confirmed by biopsy) that was not suitable for surgery were included. All tumours were less than 5 cm in diameter and almost all tumours were well or moderately differentiated. Exclusion criteria: not reported
Technique	All patients were initially treated by CXB alone. CXB was performed by delivering a 50KV beam with 0.5 mm aluminium filtration. A median total dose of 92 Gy (range – 60 to 125 Gy) was delivered in 4 or 5 sessions over a median of 57 days (range 19–195 days). The radiation output was 20 Gy per minute. If the rectal wall was not flat and supple, at the end of CXB, an iridium-192 boost of 25 Gy was delivered to the tumour bed using endoluminal 'fork' implants if the tumour was in the mid rectum, or perineal implants if the tumour was located within 6 cm of the anal margin. Surgery was performed if there was no tumour response or a recurrence was observed.
Follow-up	**Median of 5.1 years**
Conflict of interest/source of funding	None reported

Analysis

Follow-up issues: Patients had an initial follow-up appointment at 3 months. If a complete response was observed, patients were then followed up every 4 months for 2 years, then every 6 months until the fifth year. After 5 years patients were followed up annually. Authors did not state whether there were any losses to follow-up.

Study design issues: An iridium-192 boost was given to 46% (46/101) of patients. Endorectal ultrasonography was used to categorise the stage of rectal cancer in 36% (36/101) of patients. There is potential overlap with other studies included in this overview (Ortholan, 2012; Gerard, 2014 and; Gerard, 2002)

Study population issues: Polypoid tumours, with or without ulceration, were present in 69.3% (70/101) of patients. In 2 patients, tumours were located more than 10 cm from the anal margin. Tumours that invaded the anal canal were observed in 5% (5/101) of patients. Benign polyps were identified in 17% (17/101) of patients before CXB commenced: these were removed endoscopically. In 3 patients, synchronous colonic cancer was discovered and treated by hemicolectomy before or after CXB.

Other issues: A complete response was defined as the total disappearance of the tumour, with normal supple mucosa and rectal wall upon digital and proctoscopic examination. Ultimate pelvic/local control was defined as no evidence of disease at last follow-up.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **101** **Clinical response** • A 90% or more reduction in tumour size was reported in 47% (47/101) of patients 21 days after CXB commenced. • A 50% to 60% reduction in tumour size was reported in 39% (39/101) of patients 21 days after CXB commenced. • Complete remission was reported in all patients, including those who received an iridium brachytherapy boost, at 3-month follow-up. No definition of remission was provided. **Disease recurrence** • Loco-regional recurrence was reported in a total of 15% (15/101) of patients; 11 underwent salvage surgery. • Local recurrence (recurrence in the tumour bed within the field of irradiation) was reported in 8% (8/101) of patients, with a median time to recurrence of 19 months: salvage surgery was successful in 5 of these patients. • Nodal relapse (recurrence in the pararectal nodes with or without local relapse) was reported in 7% (7/101) of patients, with a median time to recurrence of 34 months: salvage surgery was successful in 5 of these patients. • Ultimate local control was reported in 99% (99/101) of patients. • Ultimate local control with rectal preservation was reported in 92% (92/101) of patients. • Distant metastases were reported in 6% (6/101) of patients. **Actuarial survival (Kaplan–Meier estimates)** • The overall survival rates were 83% and 63% at 5 and 8 years respectively. • The disease-specific survival rates were 94% and 89% at 5 and 8 years respectively • Actuarial survival rates for patients with T1 and T2 tumours were 68% and 55% respectively, at 8-year follow-up (p=0.73). • Disease-specific survival rates for patients for patients with T1 and T2 tumours were 91% and 86% respectively, at 8-year follow-up (p=0.82).	**Adverse events** • Moderate tenesmus, imperiosity or diarrhoea was reported in 15% (15/101) of patients during the course of treatment. • Ulceration of the rectal mucosa was reported in 27% (27/101) of patients at median follow-up of 4 months: all ulcerations healed with no late sequelae • Mild rectal bleeding was reported in 46% (46/101) of patients: bleeding started between 3 months and 2 years after treatment and continued for up to 4 years. **Death** • Death due to cancer (unspecified) was reported in 6% (6/101) of patients at median follow-up of 5.1 years. • Death due to intercurrent disease was reported in 15% (15/101) of patients at median follow-up of 5.1 years. • Death due to a secondary malignancy (unspecified) was reported in 2% (2/101) of patients at median follow-up of 5.1 years.
Abbreviations used: CXB, contact X-ray brachytherapy.	

Study 3 Gerard JP (2014)

Details

Study type	**Case series**
Country	France
Recruitment period	1980–2012
Study population and number	Patients with stage T1 to T3 rectal cancer **n=120 patients treated by low-energy CXB and EBRT**
Age and sex	Median age, 77 years; 71% (85/120) male
Patient selection criteria	Inclusion criteria: patients with stage T1 to T3 adenocarcinoma of the rectum, located within 10 cm of the anal verge, and accessible for digital rectal examination were included. Exclusion criteria: not reported.
Technique	Patients were initially treated by CXB followed by EBRT. CXB was performed with 10% of patients under local anaesthesia. An average total dose of 85 Gy was delivered in 3 fractions (30 Gy, 30 Gy and 25 Gy) over 4 weeks. A fourth dose of 15 Gy was delivered if necessary. EBRT commenced on day 28 of CXB and was usually performed using a 3-field technique. A total dose of 39 Gy was delivered in 13 × 3 Gy fractions. The treated volume encompassed the tumour, the mesorectum, presacral nodes and the lateropelvic nodes. EBRT was combined with concurrent chemotherapy in some patients: the total dose was 50 Gy, delivered in 2 Gy fractions over 5 weeks. In some patients, an interstitial brachytherapy boost of 20 Gy was delivered to the tumour bed using iridium-192 implants.
Than 4 cm Follow-up	**Median of 5.2 years**
Conflict of interest/source of funding	None reported

Analysis

Follow-up issues: Authors did not state whether there were any losses to follow-up.

Study design issues: The study compared clinical outcomes between 2 institutions. All patients were assessed by 1 clinician, reducing the possibility of differential misclassification. Treatment devices, doses and timings varied over time. EBRT was changed from a 2D to a 3D technique in 1993 and a different radiotherapy device was used to perform CXB from 2009. CXB and EBRT were combined with concurrent chemotherapy in 15.8% (19/120) of patients. CXB and EBRT were combined with interstitial brachytherapy in 58.3% (70/120). There is potential overlap with other studies included in this overview (Ortholan, 2012; Gerard, 1996; and Gerard, 2002)

Study population issues: The majority (55.8%; 67/120) of tumours were characterised as stage T2.

Other issues: No p values were reported for group comparisons.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 120

Overview of clinical outcomes. Numerators and denominators are stated when possible.
<table>
<tr><th>Outcome</th><th>Institution A (n=80)</th><th>Institution B (n=40)</th></tr>
<tr><td>Complete clinical response at 2 months (%)</td><td>94 (75/120)</td><td>95 (38/40)</td></tr>
<tr><td>Local recurrence at 5 years (%) *</td><td>27</td><td>14</td></tr>
<tr><td>Median time to recurrence (months)</td><td>16</td><td>17</td></tr>
<tr><td>Local control, after salvage surgery (%)</td><td>73</td><td>95</td></tr>
<tr><td>Rectal preservation at 5 years (%)</td><td>90 (72/80)</td><td>98 (39/40)</td></tr>
<tr><td>Distant metastases at 5 years (%) *</td><td>17</td><td>21</td></tr>
<tr><td>Survival at 3 years (%) *</td><td>73</td><td>60</td></tr>
<tr><td>Survival at 5 years (%) *</td><td>64</td><td>39</td></tr>
<tr><td>Disease specific survival at 3 years (%) *</td><td>86</td><td>85</td></tr>
<tr><td>Disease specific survival at 5 years (%) *</td><td>72</td><td>70</td></tr>
<tr><td>Bowel function rated good to excellent</td><td>92</td><td>79</td></tr>
</table>
* Actuarial (Kaplan–Meier) estimation
• No p values were reported</td><td>Adverse events
• Rectal bleeding was reported in up to 70% (84/120) of patients within the first 18 months of treatment. The majority of cases were treated conservatively.
• Ulceration of the rectal mucosa was reported in 33% (15/46) of patients with T3 tumours
• No incontinence, rectal stenosis or perforation was reported in any patients.</td></tr>
</table>

Study 4 Rauch P (2001)

Details

Study type	**Case series**
Country	France
Recruitment period	1978–1998
Study population and number	Patients with stage T1A to T3 rectal cancer, staged using an atypical classification system (see below). **n=97 patients treated by low-energy CXB with or without interstitial brachytherapy boost**
Age and sex	Mean age, 69 years; 60% (59/97) male
Patient selection criteria	Inclusion criteria: patients presenting with small rectal tumours, classified as T1 or T2 measuring less than 4 cm in diameter and located less than 12 cm from the anal margin were included. Exclusion criteria: patients with other forms of cancer, treated by EBRT or patients with tumours that had undergone total endoscopic or surgical resection were excluded.
Technique	Patients were initially treated by CXB followed by interstitial brachytherapy boost. CXB was performed by delivering 50 KV X-rays at a dose rate of 15 Gy per minute. A total dose of 100 Gy was delivered in 3 to 5 sessions over a 6 week period. Interstitial brachytherapy was performed 1 month after completion of CXB. A total dose of 20 Gy was delivered to the tumour bed using iridium-192 implants.
Follow-up	**10 years**
Conflict of interest/source of funding	None reported.

Analysis

Follow-up issues: No patients were lost to follow-up

Study design issues: Authors state that the inclusion criteria were extended to include elderly patients (no further details provided) with a poor health status or who had refused surgical treatments. CXB alone was used to treat 30% (29/97) of patients. CXB and interstitial brachytherapy boost were used to treat 71% (68/97) of patients.

Study population issues: Non identified

Other issues: Patients with tumour regression of 80% or more at 6 weeks after treatment commenced, and complete regression 3 weeks after the end of CXB treatment, but before interstitial brachytherapy boost, were considered to be ‘good responders’. Patients in whom a complete response was not achieved due to ulcerated or infiltrative residual disease were considered to be ‘poor responders’. Patients in whom a complete response was not achieved because of an infiltrative scar were considered to have ‘relapse’.

Rectal cancer classification

Stage	Mobility	Size (cm)	Configuration
T1A	Mobile	≤3	Polypoid
T2A	Mobile	3-5	Polypoid
T1B	Limited mobility	≤3	Polypoid or ulcerated
T2B	Limited mobility	3-5	Polypoid or ulcerated
T3	Fixed		

Key efficacy and safety findings

Efficacy

Number of patients analysed: **97**

Tumour response and local control

- A complete response was reported in 85% (82/97) of patients at median follow-up of 39 days. The remaining patients exhibited a partial response.
- 80% tumour regression was reported in 76% (74/97) of patients 6 weeks after treatment commenced.

Disease recurrence

		% (n/N)			
Clinical Stage	**n**	**Tumour recurrence**	**Nodal relapse**	**Metastatic recurrence**	**Total recurrence rate**
T1A	62	9.7 (6/62)	4.8 (3/62)	0	14.5 (9/62)
T2A	16	25 (4/16)	6.3 (1/16)	6.3 (1/16)	37.6 (6/16)
T1B	7	71.4 (5/7)	0	0	71.4 (5/7)
T2B	12	66.7 (8/12)	0	0	66.7 (8/12)
Total	97	23.7 (23/97)	41 (4/97)	1 (1/97)	28.8 (28/97)

- Local recurrences were reported in 27.8% (27/97) of patients at median follow-up of 15 months
- 16 local recurrences (tumour recurrence or nodal relapse) were treated by surgery: 2 rectal resections, 13 abdominoperineal resections and 1 endoanal excision.

Actuarial survival (Kaplan-Meier estimates)

- The actuarial survival rates were 64% and 48% at 5 and 10 years respectively.
- The disease-free survival rates were 71% and 68% at 5 and 10 years respectively.
- The disease-free survival rates for patients with T1A, T2A, T1B and T2B tumours were 86%, 60%, 28% and 37% respectively at 5-year follow-up (p=0.0001)

Safety

Adverse events

- Moderate haemorrhagic proctitis was reported in 30% (29/97) of patients. Timing of occurrence was not reported.
- Severe haemorrhagic proctitis was reported in 1 patient. Timing of occurrence was not reported.
- Ulceration of the rectal mucosa was reported in 1 patient. Timing of occurrence was not reported.
- No harmful effect on continence was reported during follow-up.

Death % (n/N)

	% (n/N)
Overall death rate	51.5% (50/97)
Intercurrent disease	26.8 (26/97)
After salvage surgery	2.1 (2/97)
Second primary cancer	3.1 (3/97)
Tumour progression	17.5 (17/97)
Unknown	2.1 (2/97)

Study 5 Christoforidis D (2009)

Details

Study type	**Case series**
Country	USA
Recruitment period	1986–2006
Study population and number	Patients with stage T1 or T2 rectal cancer **n=77 patients treated by low-energy CXB**
Age and sex	Median age, 74 years; 52% (40/77) male
Patient selection criteria	Inclusion criteria: Patients with a biopsy-proven primary rectal adenocarcinoma, classified as T1 or T2 by endorectal ultrasonography, located within 15 cm of the anal verge, and exhibiting no evidence of lymph node or distant metastasis were included. Exclusion criteria: Patients whose cancer was not characterised by endorectal ultrasonography, who underwent CXB as an adjuvant treatment after local excision, received a boost of external beam radiotherapy after CXB or were followed up for less than 6 months were excluded
Technique	All patients were initially treated by CXB alone. CXB was usually performed with the patient under conscious sedation by delivering 3 fractions of 30 Gy, at intervals of 3 to 4 weeks. In patients with an incomplete response, with a suspected residual tumour, a fourth or fifth fraction was delivered. No interstitial brachytherapy boost was given.
Follow-up	**10 years**
Conflict of interest/source of funding	None reported

Analysis

Follow-up issues: No patients were lost to follow-up

Study design issues: 1% (1/77) of patients received a total dose of 60 Gy, delivered in 2 fractions; 36% (28/77) of patients received a total dose of 120 Gy, delivered in 4 fractions; 3% (2/77) of patients received a total dose of 150 Gy, delivered in 5 fractions; and 1% (1/77) of patients received a total dose of 190 Gy, delivered in 5 fractions. The fraction dose was modified in 2 patients. One patient only received 15 Gy at the fourth session because of a device malfunction; a fifth fraction of 15 Gy was added. In another patient, with a tumour located in a difficult to reach position, the applicator slipped during irradiation. To ensure delivery of 30 Gy to the tumour, the fraction dose was increased to 40 Gy at the second session and 60 Gy at the fourth session.

Study population issues: 52% (40/77) of tumours were classified as T1, 48% (37/77) of tumours were classified as T2. The majority (64%; 49/77) of tumours were less than 3 cm in diameter. 60% (46/77) of tumours were between 6 and 10 cm from the anal verge.

Other issues: Treatment failure was defined as any persistence of disease that needed salvage surgery or as any disease recurrence (local or systemic) after a complete initial response.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 77

Clinical response
• Treatment success, following CXB alone, was reported in 73% (56/77) of patients.

Treatment failure
<table>
<tr><th></th><th>% (n/N)</th></tr>
<tr><td>Persistent/residual disease</td><td>5 (4/77)</td></tr>
<tr><td>Recurrence [a]</td><td>22 (17/77)</td></tr>
<tr><td>Overall failure rate [b]</td><td>27 (21/77)</td></tr>
</table>
[a] 12 patients had local recurrence, 3 patients had local and systemic recurrence, and 2 patients had systemic recurrence.
[b] 16 patients underwent radical salvage surgery; 10 patients were disease-free at final follow-up.
• The median time to disease recurrence was 12 months.
• No significant differences in failure rates were reported when comparisons were made according to age (≤75 years versus >75 years), stage of cancer (T1 versus T2), distance from the anal verge, tumour diameter (<3 cm versus ≥3 cm), and total irradiation dose (≤90 Gy versus > 90 Gy).

Actuarial survival (Kaplan-Meier estimates)
<table>
<tr><th></th><th colspan="2">%</th></tr>
<tr><th></th><th>5 years</th><th>10 years</th></tr>
<tr><td>Survival rate after CXB and salvage surgery</td><td>66</td><td>42</td></tr>
<tr><td>Disease-free survival rate after CXB alone</td><td>74</td><td>NR</td></tr>
<tr><td>Disease-free survival rate after CXB and salvage surgery</td><td>87</td><td>NR</td></tr>
<tr><td>Survival rate for patients with T1 cancers</td><td>69</td><td>NR</td></tr>
<tr><td>Survival rate for patients withT2 cancers</td><td>63</td><td>NR</td></tr>
</table>
• There was no significant difference in the survival rates of patients with T1 cancers compared against patients with T2 cancers (p=0.718)
</td><td>
• Symptomatic proctitis with tenesmus, diarrhoea or pain was reported in 13% (10/77) of patients. Time of occurrence was not reported.
• Rectal bleeding that was treated conservatively was reported in 12% (9/77) of patients. Timing of occurrence was not reported.
• Rectal bleeding that needed hospitalisation, transfusion or surgical intervention was reported in 8% (6/77) of patients. Timing of occurrence was not reported.
• Coccygeal fracture was reported in 1 patient. Timing of occurrence was not reported. Authors do not make it clear if this was directly related to the procedure.
</td></tr>
<tr><td colspan="2">Abbreviations used: CXB, contact X-ray brachytherapy; NR, not reported.</td></tr>
</table>

Study 6 Gerard JP (2002)

Details

Study type	**Case series**
Country	France
Recruitment period	1986–1998
Study population and number	Patients with stage T2 or T3 rectal cancer **n=63 patients treated by low-energy CXB followed by EBRT and interstitial brachytherapy boost**
Age and sex	Median age, 72 years; 73% (46/63) male
Patient selection criteria	Inclusion criteria: Patients with histologically confirmed adenocarcinoma of the lower rectum which believed to be stage T2 or T3, and located within 6 cm of the anal verge were included. All patients were considered to show no signs of distant metastasis and were judged to need an abdominoperineal resection. Exclusion criteria: patients with polypoid tumours classified as T1, tumours involving more than two-thirds of the circumference of
Technique	Patients were initially treated by CXB followed by EBRT and interstitial brachytherapy boost. CXB was performed by delivering a 50 KV photon beam with 0.5 mm aluminium filtration. A median total dose of 80 Gy was delivered in 3 fractions: on days 1, 7 and 21 respectively. On day 14 of the CXB treatment, EBRT was started using 18 MV photons. The total dose administered was 39 Gy in 13 fractions, delivered over 17 days. The target volume/area included the primary rectal tumour, the hypogastric vessels and the perirectal nodes, up to the S1-S2 junction: the S2-S3 junction was used for very frail patients. Interstitial brachytherapy was performed 4 to 6 weeks after completion of EBRT. A median dose of 20 Gy was delivered to the tumour bed using iridium-192 implants that were inserted for 22 hours.
Follow-up	**Median of 4.5 years**
Conflict of interest/source of funding	None reported

Analysis

Follow-up issues: No patients were lost to follow-up

Study design issues: No statistical tests were used in the analyses. Most (89%; 56/63) of tumours were classified using endorectal ultrasonography. Patients with enlarged perirectal lymph nodes were not excluded. EBRT was not performed in 3 patients. Interstitial brachytherapy boost was not performed in 7 patients. There is potential overlap with other studies included in this overview (Ortholan, 2012; Gerard, 2014; and Gerard, 1996)

Study population issues: Authors state that severe comorbidity was present in 57% (36/63) of patients; these included cardiorespiratory insufficiency, neurologic deficit, diabetes, or severe obesity. Between 2 and 4 perirectal metastatic nodes were identified in 6.3% (4/63) of patients.

Other issues: None identified

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 63

Tumour response
• A complete clinical response was reported in 92% (58/63) of patients at 2-month follow-up.
• A small residual tumour was reported in 8% (5/63) of patients at 2-month follow-up: biopsy showed residual adenocarcinoma in all cases.

Local pelvic control
• The local control rate, after radiotherapy treatment, was 63% (40/63) at median follow-up of 4.5 years.
• The local control rate, after radiotherapy and salvage surgery, was reported in 73% (46/63) at median follow-up of 4.5 years.

Disease recurrence (tumour recurrence in the tumour bed after a clinically complete response)
• Local recurrence was reported in 28.5% (18/63) of patients at median follow-up of 54 months: median time to recurrence was 16 months.
• Nodal relapse was reported in 2 patients: 1 patient survived following salvage surgery.
• In 5 patients an abdominoperineal resection was possible, leading to ultimate local control
• A palliative colostomy was needed in 2 patients.

Actuarial survival rates at 5 years (Kaplan-Meier estimates)
<table>
<tr><th></th><th>n</th><th>%</th></tr>
<tr><td>Overall survival rate</td><td>63</td><td>64.4</td></tr>
<tr><td>Age</td><td></td><td></td></tr>
<tr><td>Patients aged ≤78</td><td>46</td><td>78</td></tr>
<tr><td>Patients aged >80</td><td>17</td><td>0</td></tr>
<tr><td>Tumour diameter</td><td></td><td></td></tr>
<tr><td>2–2.9 cm</td><td>20</td><td>82.4</td></tr>
<tr><td>3–3.9 cm</td><td>17</td><td>72.7</td></tr>
<tr><td>≥4.0</td><td>24</td><td>41.5</td></tr>
<tr><td>Circumference</td><td></td><td></td></tr>
<tr><td>≤33 %</td><td>35</td><td>74.5</td></tr>
<tr><td>34–50%</td><td>24</td><td>58.6</td></tr>
<tr><td>50%</td><td>4</td><td>0</td></tr>
<tr><td>T stage</td><td></td><td></td></tr>
<tr><td>T2</td><td>40</td><td>81.9</td></tr>
<tr><td>T3</td><td>22</td><td>34.6</td></tr>
<tr><td>Morphology</td><td></td><td></td></tr>
<tr><td>Polypoid ulceration</td><td>20</td><td>85.7</td></tr>
<tr><td>Fungating</td><td>34</td><td>51.4</td></tr>
<tr><td>Flat/other</td><td>9</td><td>75</td></tr>
</table>
</td><td>
• No early toxicity, attributable to CXB, was reported.
• Rectal bleeding was reported in 38.1% (24/63) of patients 6 months after treatment. Bleeding lasted for up to 3 years. Patients were treated by medication or argon plasma coagulation. Only 1 patient needed occasional blood transfusions.
• Authors reported that ‘grade 2 rectal necrosis’ occurred in 19% (12/63) of patients at a median of 7 months after treatment. Details about the type and severity of necrosis were not provided. Authors stated that some patients had rectal necrosis which was accompanied by urgency and minor soiling. They highlighted that necrosis healed within 3 to 6 months in all patients.
</td></tr>
</table>

Study 7 Mendenhall (1997)

Details

Study type	**Non-randomised comparative study**
Country	USA
Recruitment period	1974–1994
Study population and number	Patients with T1 toT3 rectal cancer **n=65 patients (20 low-energy CXB alone versus 45 wide local excision and external beam radiotherapy [EBRT])**
Age and sex	Age and sex ratio not reported
Patient selection criteria	Inclusion criteria: patients with early staged lesions that were moderately differentiated, mobile, exophytic, and ≤3 cm in diameter were included Exclusion criteria: patients with gross residual disease that received subsequent salvage surgery, such as abdominoperineal resection were excluded
Technique	CXB was performed by delivering a total dose of 110 to 120 Gy in 3 or 4 sessions over 30 to 56 days. Wide local excision was usually performed using a transanal approach. Postoperative EBRT was initiated 3–6 weeks after surgery. EBRT was performed by delivering a total dose of 45 to 60 Gy in multiple 1.6 Gy fractions
Than 4 cm Follow-up	**Median of 5.1 years**
Conflict of interest/source of funding	None reported

Analysis

Follow-up issues: Authors state that all patients were followed-up for at least 2 years or until death. Authors did not state whether there were any losses to follow-up.

Study design issues: patients were either given CXB alone or wide local excision followed by external beam radiotherapy depending on the inclination of the attending surgeon: patients who had lesions that were not ideal for local therapy alone were treated by local excision an EBRT. Authors state that patients with gross residual disease who had subsequent salvage surgery, such as abdominoperineal resection, were excluded from analyses. Eleven patients treated by wide local excision and EBRT had an interstitial brachytherapy boost using iridium-192 implants.

Study population issues: Authors state that patients treated by wide local excision and radiotherapy tend to have unfavourable lesions and are not comparable to those treated by patients treated by CXB alone. Patients treated by wide local excision and EBRT had equivocal tumour margins (n=29), invasion of the muscularis propria (n=8), microscopically positive margins (n=6), fragmented excision (n=5), close margins ≤5 mm (n=3), perineural invasion (n=1).

Other issues: Loco-regional failure/recurrence was defined as recurrence of cancer in the pelvis region, either at the primary tumour site or in the regional lymph nodes.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 65 (20 CXB alone versus 45 Wide local excision and EBRT)

Overview of efficacy outcomes
<table>
<tr><th></th><th>CXB alone</th><th>Wide local excision and EBRT</th></tr>
<tr><td>Local control rate at 5 years (%) a</td><td>85</td><td>92</td></tr>
<tr><td>Local recurrence (%)</td><td>15 (3/20) b</td><td>11 (5/45) b</td></tr>
<tr><td>Local control with sphincter preservation (%) a</td><td>80</td><td>84</td></tr>
<tr><td>Distant metastases (%)</td><td>5 (1/20)</td><td>4 (2/45)</td></tr>
<tr><td>Overall survival rate at 5 years (%) a</td><td>76</td><td>80</td></tr>
<tr><td>Disease specific survival rate at 5 years (%) a</td><td>84</td><td>88</td></tr>
</table>
[a] Actuarial rate based on the life-table approach
[b] All patients had recurrence at the primary tumour site: no patients had a nodal failure.</td><td>Adverse events
• No acute toxicity was observed in patients treated by CXB alone.
• Rectal bleeding was reported in 10% (2/20) patients treated by CXB alone. One patient was treated by laser coagulation whereas another patient needed a blood transfusion.
• Soft tissue necrosis that resolved with medical treatment was reported in 1 patient who was treated by CXB alone.</td></tr>
<tr><td colspan="2">Abbreviations used: CXB, contact X-ray brachytherapy; EBRT, external beam radiotherapy.</td></tr>
</table>

Study 8 Papillon J C (1992)

Details

Study type	**Case series**
Country	France
Recruitment period	1951–1984
Study population and number	Patients with stage T1 or T2 rectal cancer **n=312 patients treated by low-energy CXB and interstitial brachytherapy boost**
Age and sex	Mean age, 65 years; sex ratio not reported.
Patient selection criteria	Inclusion criteria: Patients with invasive, sessile, well differentiated or moderately well differentiated adenocarcinoma of the rectum (graded T1 or T2) were included. Exclusion criteria: Not reported.
Technique	Patients were initially treated by CXB followed by interstitial brachytherapy boost. CXB was performed by delivering a total dose of 100 Gy to 120 Gy of radiation in 4 sessions (20 to 30 Gy per session) over a 6-week period. Four to six weeks after completion of CXB, interstitial brachytherapy boost with iridium-192 was performed to deliver a booster dose of 20 Gy to the tumour bed. A steel fork with 2 prongs, each 4 cm long and 16 mm apart that was preloaded with iridium-192 was implanted into the rectum for 24 hours.
Follow-up	**5 years**
Conflict of interest/source of funding	None reported

Analysis

Follow-up issues: No patients were lost to follow-up

Study design issues: None identified

Study population issues: Authors state that 66.6% (209/312) of patients had polypoid protuberant tumours and 33.3% (103/312) of patients had ulcerative lesions.

Other issues: None identified

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **312** **Clinical response** • Pelvic recurrence was reported in 8% (26/312) of patients: • Local failure/recurrence was reported in 4.5% (14/312) of patients and nodal relapse was reported in 3.8% (12/312) of patients. Seven patients survived following salvage surgery. • Disease-free survival was reported in 74% (231/312) of patients at 5-year follow-up. Of the 231 patients who survived, 96% (223/231) of patients had normal anal function (no further details provided) • A permanent colostomy was needed in 3% (8/312) of patients	**Adverse events** • Superficial radionecrosis was reported in 5% (16/312) of patients. Authors stated that most cases healed spontaneously (no figures reported). • Slight proctitis was reported in 10% (32/312) of patients. Timing of occurrence was not reported • Death due to cancer (unspecified) was reported in 8% (24/312) of patients at 5-year follow-up: 7 of these deaths were due to distant metastasis without pelvic disease. • Death due to intercurrent disease was reported in 17% (53/312) of patients at 5-year follow-up. • Postoperative death, after abdominoperineal resection, was reported in 1% (4/312) of patients at 5-year follow-up.

Study 9 Hull T (1999)

Details

Study type	**Case series**
Country	USA
Recruitment period	1973–1993
Study population and number	Patients with stage T1 or T2 rectal cancer **n=126 patients treated by low-energy CXB**
Age and sex	Mean age, 66 years; 65% (82/126) male
Patient selection criteria	Inclusion criteria: not reported Exclusion criteria: patients with tethered lesions, palpable lymph nodes, tumours greater than 5 cm in diameter, a diagnosis other than adenocarcinoma, who were previously treated by external-beam radiotherapy (EBRT), or who did not respond after 2 sessions of CXB were excluded.
Technique	All patients were initially treated by CXB alone. CXB was performed by delivering 2000 to 4000 rads per treatment session, every 3 weeks, for 3 or 4 sessions.
Follow-up	**Mean of 6.8 years**
Conflict of interest/source of funding	None reported

Analysis

Follow-up issues: Post-treatment, patients were followed up monthly. If there was no suspicion of recurrence after 4 visits, follow-up frequency was extended to every 3 months. After 2 years, the examinations were extended to every 6 months. After 5 years, the patients were examined annually. Authors did not state whether there were any losses to follow-up.

Study design issues: Potential for selection bias because only patients who responded to treatment after 2 CXB treatments were included in the study.

Study population issues: None identified

Other issues: None identified

Key efficacy and safety findings

Efficacy

Number of patients analysed: **126**

Disease recurrence

	% (n/N)	Mean tumour size (cm)	Mean distance from the anal verge (cm)
Recurrence	29 (37/126)	2.5	5.2
No recurrence	71 (89/126)	2.3	5.7

- Mean time to recurrence was 16.08 months.
- Distant recurrence was reported in 8% (10/126) of patients.
- Local recurrence was reported in 21% (27/126) of patients.
- A second treatment, curative or palliative, was given to 84% (31/37) of patients with disease recurrence: Of these patients, 45% (14/31) were alive with no evidence of disease at final follow-up.

Safety

Adverse events

- Actinic ulcers, at treatment sites, were reported in 100% (126/126) of patients.
- Death due to cancer was reported in 12% (15/126) of patients

Study 10 Hershman MJ (2003)

Details

Study type	**Non-randomised comparative study**
Country	United kingdom
Recruitment period	1992–2002
Study population and number	Patients with stage T1 to T3 rectal cancer **n=100 patients (29 radical radiotherapy versus 25 local excision and postoperative radiotherapy versus 33 preoperative radiotherapy and local excision versus 13 surgery alone)**
Age and sex	Median age, 73 years; 65% (55/100) male
Patient selection criteria	Inclusion criteria: Patients with a mobile tumour with no evidence of lymph node metastases were included Exclusion criteria: Not reported
Technique	Patients were divided into 4 groups: **Group A:** Radical radiotherapy: patients received low-energy CXB alone or external beam radiotherapy [EBRT] followed by CXB boost. **Group B:** Surgery and postoperative radiotherapy. Patients underwent local excision followed by EBRT and a CXB boost. **Group C:** Preoperative EBRT or chemoradiotherapy plus surgery. Patients received preoperative radiotherapy or chemoradiotherapy followed by local excision. **Group D:** Surgery alone. Patients underwent local excision alone. **Surgery:** Patients underwent local excision by endoscopic resection or transanal endoscopic microsurgery. Transanal endoscopic microsurgery was achieved by placing a 10 mm margin around the tumour and performing a full-thickness excision. Anteriorly-placed tumours, located above the peritoneal reflection, were removed by partial-thickness resection. **CXB:** No details were provided. **EBRT:** The procedure was performed using either a 3 or 4 field technique. Patients received a total dose of 39 Gy delivered in 13 fractions over 2 weeks or 45 Gy delivered in 20 fractions over 4 weeks. **Chemotherapy:** consisted of continuous 5 GU infusion 1G/m2 on days 1–4 in weeks 1 and 4 of treatment. No further details were provided.
Follow-up	**Up to 5 years**
Conflict of interest/source of funding	None reported

Analysis

Follow-up issues: Authors did not state whether there were any losses to follow-up.

Study design issues: The paper is unclear about the specific treatment received by patients and the stage at which treatment was received. For example, in the radical-radiotherapy group, authors stated that 12 patients were treated by CXB alone and the remaining patients (n=17) underwent EBRT or chemoradiotherapy. They then stated that 26 patients in this group were offered CXB boost with 1 patient having a further boost of interstitial brachytherapy. There were similar uncertainties about the number of patients treated by local excision and postoperative radiotherapy. One of the authors was contacted to seek clarification. It was ascertained that CXB (alone or as an adjuvant treatment) was given to all patients in the radical radiotherapy group. Authors also confirmed that all patients who received postoperative radiotherapy were given EBRT followed by CXB boost.

Study population issues: None identified

Other issues: No p values were reported.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 100 (29 CXB alone or EBRT plus CXB versus 25 local excision plus EBRT plus CXB boost versus 33 EBRT or chemoradiotherapy plus local excision versus 13 local excision alone)

Disease recurrence
<table>
<tr><th>Outcome</th><th>Group A (n=29)</th><th>Group B (n=25)</th><th>Group C (n=33)</th><th>Group D (n=13)</th></tr>
<tr><td>Local recurrence (%) [n/N]</td><td>10 [3/29]</td><td>8 [2/25]</td><td>12 [4/33]</td><td>8 [1/13]</td></tr>
<tr><td>Distant metastases</td><td>NR</td><td>NR</td><td>3 [1/33]</td><td>NR</td></tr>
<tr><td>Cancer-specific survival (%)</td><td>97</td><td>96</td><td>94</td><td>92</td></tr>
<tr><td>Overall survival (%)</td><td>79</td><td>92</td><td>74</td><td>NR</td></tr>
</table>
NR-Not reported
Group A – CXB-alone or EBRTplus CXB
Group B – local excision plus EBRT plus CXB boost
Group C - EBRT or chemoradiotherapy plus local excision
Group D – local excision alone</td><td>Adverse events
• Proctitis, leading to rectal bleeding, was reported in 6.8% (2/29) of patients in the radical radiotherapy group.
• Death due to colorectal cancer was reported in 3%, 4%, 6% and 8% of patients in the radical radiotherapy, local excision plus EBRT plus CXB boost, EBRT or chemoradiotherapy plus local excision, and local excision-alone groups, respectively.</td></tr>
<tr><td colspan="2">Abbreviations used: CXB, contact X-ray brachytherapy; EBRT, external beam radiotherapy</td></tr>
</table>

Efficacy

Actuarial survival (Kaplan–Meier estimates)

In a randomised controlled trial of 88 patients treated by both low-energy CXB and external beam radiotherapy (EBRT; n=45) or EBRT alone (n=43), overall actuarial survival rates were 55% and 56% respectively, at 10-year follow-up (p=0.85). In the same study, disease-free survival rates were 53% and 54% respectively, at 10-year follow-up (p=0.99)[1].

In a case series of 101 patients treated by low-energy CXB with or without interstitial brachytherapy boost, overall actuarial survival rates were 83% and 63% at 5 and 8 years, respectively. In the same study, disease-specific survival rates were 94% and 89% at 5 and 8 years, respectively. Actuarial survival rates for patients with T1 and T2 tumours were 68% and 55%, respectively, at 8-year follow-up (p=0.73). Disease-specific survival rates for patients for patients with T1 and T2 tumours were 91% and 86%, respectively, at 8-year follow-up (p=0.82)[2].

In a case series of 77 patients treated by low-energy CXB with or without salvage surgery, the actuarial survival rates were 66% and 42% at 5 and 10 years respectively[5].

In a case series of 63 patients treated by low-energy CXB followed by EBRT and interstitial brachytherapy boost, the overall actuarial survival rate was 64.4% at 5-year follow-up. In the same study, the survival rates of patients with tumour diameters between 2 and 2.9 cm, 3 and 3.9 cm and tumours over 4 cm were 82%, 73% and 42% respectively, at 5-year follow-up (no p values reported). The survival rates of patients with T2 and T3 tumours were 82% and 35% respectively, at 5-year follow-up (no p value reported)[6].

Tumour/clinical response

In the randomised controlled trial of 88 patients treated by low-energy CXB and EBRT (n=45) or EBRT alone (n=43), a complete clinical response (no visible tumour; rectal mucosa clinically and endoscopically normal; or simple scar without suspicious induration) was reported in 26% (11/43) of patients in the low-energy CXB and EBRT group and 33% (12/36) of patients in the EBRT-alone group at 5-week follow-up (no p value reported). In the same study, a clinical response greater than 50% (>50% reduction in the product of 2 perpendicular parameters) was reported in 69% (29/42) of patients in the low-energy CXB and EBRT group and 67% (24/36) of patients in the EBRT-alone group at 5-week follow-up (no p value reported)[1].

In a case series of 97 patients treated by low-energy CXB with or without interstitial brachytherapy boost, a complete response (no definition provided) was reported in 85% (82/97) of patients at a median follow-up of 39 days[4].

In the case series of 63 patients treated by low-energy CXB followed by EBRT and interstitial brachytherapy boost, a complete clinical response (no definition provided) was reported in 92% (58/63) of patients at 2-month follow-up[6].

Disease recurrence

In the randomised controlled trial of 88 patients treated by low-energy CXB and EBRT (n=45) or EBRT alone (n=43), actuarial local recurrence rates (Kaplan–Meier estimates) were 10% and 15% respectively, at 10-year follow-up (p=0.69). Distant recurrence was reported in 27% (12/45) of patients in the low-energy CXB and EBRT group and 26% (11/43) of patients in the EBRT-alone group at 10-year follow-up (no p value reported)[1].

In the case series of 101 patients treated by low-energy CXB with or without interstitial brachytherapy boost, loco-regional recurrence was reported in 15% (15/101) of patients: local recurrence in 8% (8/101) of patients and nodal relapse in 7% (7/101) of patients[2].

In the case series of 63 patients treated by low-energy CXB followed by EBRT and interstitial brachytherapy boost, local recurrence was reported in 29% (18/63) of patients at median follow-up of 54 months[6].

In a case series of 126 patients treated by low-energy CXB alone, disease recurrence was reported in 29% (37/126) of patients: the mean time to recurrence was 16.08 months. Local recurrence was reported in 21% (27/126) of patients whereas distant recurrence was reported in 8% (10/126) of patients. A second treatment, curative or palliative, was given to 84% (31/37) of patients with disease recurrence: 45% (14/31) of these patients were alive with no evidence of disease at final follow-up[9].

Sphincter saving procedures and colostomy

In the randomised controlled trial of 88 patients treated by low-energy CXB and EBRT (n=45) or EBRT alone (n=43) all patients underwent surgery (either sphincter saving procedures or abdominoperineal resections) after initial treatment. Sphincter-saving procedures were possible in 76% (34/45) of patients in the low-energy CXB and EBRT group and 44% (19/43) of patients in EBRT-alone group (no p values reported). Abdominoperineal resections were needed in 24% (11/45) of patients in the low-energy CXB and EBRT group and 56% (24/43) of patients in EBRT-alone group (no p values reported). In the same study, the actuarial colostomy rates (Kaplan–Meier estimates) were 29% in the low-energy CXB and EBRT group and 63% in the EBRT-alone group at 10-year follow-up ($p<0.001$)[1].

In the case series of 101 patients treated by low-energy CXB with or without interstitial brachytherapy boost, salvage surgery was needed in 11% (11/101) of patients after loco-regional recurrence[2].

In a case series of 77 patients treated by low-energy CXB, radical salvage surgery (no further details provided) was needed in 21% (16/77) of patients: 10 of these patients were disease free at final follow-up[5].

In a case series of 312 patients treated by low-energy CXB and interstitial brachytherapy boost, a permanent colostomy was needed in 3% (8/312) of patients following abdominoperineal resection[8].

Safety

Death

Death due to colorectal cancer was reported in 24% (11/45) of patients treated by low-energy CXB and EBRT and 28% (12/43) of patients treated by EBRT alone, at 10-year follow-up, in the randomised controlled trial of 88 patients [1].

Death due to tumour progression was reported in 18% (17/97) of patients, at 10-year follow-up, in a case series of 97 patients treated by low-energy CXB with or without interstitial brachytherapy boost[4].

Death due to colorectal cancer was reported in 3%, 4%, 6% and 8% of patients in the radical radiotherapy (low-energy CXB alone or CXB and EBRT), local excision followed by EBRT and low-energy CXB, EBRT or chemoradiotherapy followed by local excision, and local excision-alone groups respectively, at follow-up of up to 5 years in a non-randomised comparative study of 100 patients[10].

Rectal bleeding

Mild rectal bleeding was reported in 46% (46/101) of patients in the case series of 101 patients treated by low-energy CXB with or without interstitial brachytherapy boost: bleeding started between 3 months and 2 years after treatment and continued for up to 4 years[2].

Rectal bleeding was reported in 38% (24/63) of patients, 6 months after treatment, in the case series of 63 patients treated by low-energy CXB followed by EBRT and interstitial brachytherapy boost. Bleeding lasted for up to 3 years. Patients were treated by medication or argon plasma coagulation. Only 1 patient needed occasional blood transfusions[6].

Proctitis

Slight proctitis was reported in 10% (32/312) of patients in the case series of 312 patients treated by low-energy CXB and interstitial brachytherapy boost: timing of occurrence was not reported[8].

Rectal necrosis

Authors reported that ‘grade 2 rectal necrosis’ occurred in 19% (12/63) of patients, at a median of 7 months after treatment, in the case series of 63 patients treated by low-energy CXB followed by EBRT and interstitial

brachytherapy boost. Details about the type of grading system for rectal necrosis were not provided. Authors stated that some patients had rectal necrosis which was accompanied by urgency and minor soiling. They highlighted that necrosis healed within 3 to 6 months in all patients[6].

Superficial radionecrosis was reported in 5% (16/312) of patients treated by low-energy CXB and interstitial brachytherapy boost: timing of occurrence was not reported. The authors stated that most cases healed spontaneously (no figures provided) [8].

Ulceration of the rectal mucosa

Ulceration of the rectal mucosa was reported in 27% (27/101) of patients, at a median follow-up of 4 months, in the case series of 101 patients treated by low-energy CXB with or without interstitial brachytherapy boost: all ulcerations healed with no late sequalae[2].

Other adverse events

Moderate tenesmus, imperiosity (urgency of bowel movement) or diarrhoea was reported in 15% (15/101) of patients, during the course of treatment, in the case series of 101 patients treated by low-energy CXB with or without interstitial brachytherapy boost[2].

A coccygeal fracture was reported in 1 patient in the case series of 77 patients treated by low-energy CXB: timing of occurrence was not reported. Authors do not make it clear if this was directly related to the procedure[5].

Validity and generalisability of the studies

- Most studies highlight that low-energy CXB is usually done in combination with other types of treatment [1,2,3,4,6,7,8,10].
- There may be considerable overlap in the patient populations of some studies included in table 2 [1,2,3,6].
- The authors did not state whether there were any losses to follow-up in most of the studies included in table 2 [1,2,3,7,9,10]
- Seven studies in table 2 included patients who had T3 rectal tumours[1,2,3,4,6,7,10].

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). Available from 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 low-energy contact X-ray brachytherapy (the Papillon technique) for early-stage rectal cancer were submitted and can be found on the NICE website; https://www.nice.org.uk/guidance/GID-IP1234/documents/lowenergy-contact-xray-brachytherapy-the-papillon-technique-for-earlystage-rectal-cancer-saqs2

Patient commentators' opinions

NICE's Public Involvement Programme sent 60 questionnaires to 4 NHS trusts for distribution to patients who had the procedure (or their carers). NICE received 43 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

- No ongoing trials were identified in clinical trial databases. One specialist adviser highlighted that the International Contact Radiotherapy Society is planning a randomised controlled trial, the Organ Preservation for Early Rectal Adenocarcinoma (OPERA) trial that will start in 2015 and finish in 2018.

References

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Appendix A: Additional papers on low-energy contact X-ray brachytherapy (the Papillon technique) for early-stage 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
Gerard JP1, Chapet O, Nemoz C. (2004) Improved sphincter preservation in low rectal cancer with high-dose preoperative radiotherapy: the lyon R96-02 randomized trial. J Clin Oncol. 22(12):2404-9.	Randomised controlled trial n=88 (45 CXB + External Beam Radiotherapy [EBRT] & vs 43 EBRT-alone) Follow-up: 2 years	Sphincter saving procedures were possible in 76% of patients in the low-energy CXB+EBRT group and 44% of patients in the EBRT-alone group (p=0.004). Recurrence-free survival rates were 88% in the CXB+EBRT group and 92% in the EBRT-alone group at 2 year follow-up. Pelvic local recurrence was reported in 2% (1/45) of patients in the CXB+EBRT group and 7% (3/43) of patients in the EBRT-alone group. Death due to cancer was reported in 6% (3/45) of patients in the CXB+EBRT group and 16% (7/43) of patients in the EBRT-alone group at 2 year follow-up.	The outcomes of this group of patients are reported in a another paper by the same author which is included in table 2 (Ortholan, 2012)
Papillon J. (1990) Present status of radiation therapy in the conservative management of rectal cancer. Radiother Oncol. (4): 275-83.	Case series n=310 Follow-up: minimum of 3 years	The disease-specific survival rate was 74% at 5 years. Local failures were reported in 4.5% (14/310) of patients. Nodal failures were reported in 3.8% (12/310) of patients. Death by cancer was reported in 11% and 16% of patients at 3 and 5 years, respectively	The outcomes of this group of patients are reported in a another paper by the same author which is included in table 2 (Papillon, 1992)
Papillon J. (1974) Endocavitary irradiation in the curative treatment of early rectal cancers. Diseases of the colon and rectum. 17 (2): 172-80	Case series n=106 Follow-up: 5 years	Disease-free survival was 70% (75/106) at 5 year follow-up. Local failure was reported in 13.2% (14/106) of patients. Radical surgery was required in 11.3% (12/106) of patients. Distant metastases were	Few outcome measures were reported. Larger studies, by the same author, that reported similar outcomes are included in table 2.

		reported in 7.5% (8/106) of patients.	
Sun Myint A, Grieve RJ, McDonald AC, et al. (2007) Combined modality treatment of early rectal cancer: the UK experience. Clin Oncol (R Coll Radiol) 19 (9): 674-81	Case series n=220 Follow-up: median of 4.6 years	Residual disease was reported in 11% (24/220) of patients after initial radiotherapy: immediate rescue surgery was needed for 21 of these patients. Late recurrences were required in 10% (22/220) of patients: The survival rate was 71% at a median of 4.6 months after treatment.	124 of the 220 patients were treated by CXB; however, the clinical outcomes of these patients were not explicitly reported. Instead, authors reported the results of all patients treated using a multimodality approach
Maignon P, Guerif S, Darsonni R (1998) Conservative management of rectal adenocarcinoma by radiotherapy. Int. J. Radiation Oncology Biol. Phys. 40 (5): 1077-85	Case series n=151 Follow-up: 5 years	The actuarial survival rate for patients treated by radical radiotherapy (EBRT and/or CXB and/or interstitial brachytherapy) was 57% at 5 year follow-up. The disease-free survival rate for patients treated by radical radiotherapy was 66% at 5 year follow-up. Pelvic failure was reported in 13% (8/61) of patients with tumours <3cm who were treated by CXB-alone. Pelvic failure was reported in 28% (9/32) of patients with tumours >3cm who were treated by CXB-alone.	129 of the 151 patients were treated by CXB; however, the clinical outcomes of these patients were not explicitly reported. Instead, authors reported the results of all patients treated using radical radiotherapy (EBRT and/or CXB and/or interstitial brachytherapy)
Birnbaum EH, Ogunbiyi OA, Gagliardi G (1999) Selection criteria for treatment of rectal cancer with combined external and endocavitary radiation. 42(6): 727-33	Case series n=72 Follow-up: median of 31 months.	The actuarial survival rate was 89% and 67% at 2 and 5 year follow-up, respectively. Salvage surgery was required in 23.6% (17/72) of patients. Distant metastases occurred in nine patients; all had pelvic recurrences, and six died of disease. Mobile lesions recurred less than tethered lesions (26 vs. 52 percent; P = 0.048). Transrectal ultrasound stage was predictive of recurrence (0 percent uT1, 22 percent uT2, and 51 percent uT3; P = 0.015).	Larger studies that reported similar outcomes are included in table 2. Furthermore the study aimed to discuss and identify predictive factors associated with tumour recurrence.
Roth SL, Horiot JC, Calais G, et al. (1988) Results of endocavitary irradiation of early rectal	Case series n=91	Preservation of the sphincter was obtained in 85% (77/91). The actuarial local relapse-	Larger studies that reported similar outcomes are included

tumours. Acta Oncol. 27 (6b): 825-7.	Follow-up: 5 years	free survival rate at 5 years was 74% (67/91). No significant difference was seen between the 72 adenocarcinomas and 19 villous adenomas (p = 0.12). For the middle rectum the rate was 94% compared to 54% for the upper and 77% for the lower rectum. Anterior primaries fared better than posterior and lateral tumours (100%, 63%, and 67% respectively). After salvage therapy the local control rate raised to 91% (83/91).	in table 2.
Roth SL, Horiot JC, Calais G, et al. (1989) Prognostic factors in limited rectal cancer treated with intracavitary irradiation. Int J Radiat Oncol Biol Phys. 16(6):1445-51.	Case series n=91 Follow-up: 5 years	Local control was achieved in 91% (83/91) of patients. Sphincter preservation was obtained in 85% (77/91) of patients. "De novo" adenocarcinomas developed on pre-existing benign pathology and villous adenomas were not significantly different with regard to local control (76% resp. 75% versus 59.5%; p = 0.22).	Few outcome measures were reported. Larger studies that reported similar outcomes are included in table 2.
Lavery IC, Jones IT, Weakley FL, et al. (1987) Definitive management of rectal cancer by contact (endocavitary) irradiation. Dis Colon Rectum. 30 (11): 835-8	Case series n=62 Follow-up: 10 years	Disease-free survival was reported in 90% (56/62) of patients. Local recurrence was reported in 18% (11/62) of patients. Local recurrence was reported in 24.1% (15/62) of patients. Distant metastases were reported in 6.4% (4/62) of patients.	Larger studies that reported similar outcomes are included in table 2.
Sischy B, Hinson EJ, Wilkinson DR. (1988) Definitive radiation therapy for selected cancers of the rectum. Br J Surg. 75 (9): 901-3.	Case series n=192 patients (treated with curative intent) Follow-up: 5 years	Local control was achieved in 91% (183/192) of patients. Local recurrence was reported in 4.7% (9/192) of patients: 5 of these patients had salvage surgery. Death due to intercurrent disease was reported in 23.4% (45/192) of patients. Cure was achieved in 93% (74/80) of patients who were followed up for more than 5 years.	Few outcome measures were reported. Larger studies that reported similar outcomes are included in table 2.

Kovalic JJ (1988) Endocavitary irradiation for rectal cancer and villous adenomas. Int J Radiat Oncol Biol Phys. 14 (2): 261-4	Case series n=52 Follow-up: 3 years	Disease free survival rates for patients with invasive carcinomas were 90.4%, 78.6% and 74.2% at 1,2 and 3 years, respectively. Disease free survival rates for patients with villous adenomas were 80.4%, 60.3% and 45.2% at 1,2 and 3 years, respectively.	Larger studies that reported similar outcomes are included in table 2. It was unclear if CXB was performed. Authors stated that patients were treated by endocavitary irradiation; however, they did not explicitly describe what technique was performed.
Gerard JP, Roy P, Coquard R, et al. (1996) Combined curative radiation therapy alone in (T1) T2-3 rectal adenocarcinoma: a pilot study of 29 patients. Radiother Oncol. 38(2):131-7.	Case series n=29 Follow-up: median of 46 months	Overall and specific survival at 5 years was 68% and 76%. Local control was obtained in 21/29 patients (72%). Grade 2 rectal necrosis was reported in 17.2% (5/29) of patients. Rectal bleeding was reported in 1 patient.	Larger studies that reported similar outcomes are included in table 2.
Gerard JP, Chapet O, Ortholan C, et al. (2007) French experience with contact X-ray endocavitary radiation for early rectal cancer. Clinical Oncology. 19(9):661-73	Review	In early rectal cancer, CXB can play an important role in three different situations: (1) small T1 less than 2 cm: adjuvant CXB after local excision; (2) T2 N0 or large T1: first-line CXB combined with external beam radiotherapy (+/- chemotherapy) followed by surgery (anterior resection or local excision); (3) early T3 N0 in frail patients: the same approach as for T2 N0 with, in case of clinical complete response, local excision or follow-up.	Reviews would not normally be included in table 2 of the overview. This paper outlines the treatment techniques and results of clinical studies of patients treated by CXB.

Appendix B: Related NICE guidance for low-energy contact X-ray brachytherapy (the Papillon technique) for early-stage rectal cancer

Guidance	Recommendations
Interventional procedures	**Preoperative high dose rate brachytherapy for rectal cancer. NICE interventional procedure guidance 201 (2006)** 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 guidance 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 three 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 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 low-energy contact X-ray brachytherapy (the Papillon technique) for early-stage rectal cancer

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	25/03/2015	Issue 3 of 12, March 2015
HTA database (Cochrane Library)	25/03/2015	Issue 1 of 4, January 2015
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	25/03/2015	Issue 2 of 12, February 2015
MEDLINE (Ovid)	25/03/2015	1946 to March Week 3 2015
MEDLINE In-Process (Ovid)	25/03/2015	March 24, 2015
EMBASE (Ovid)	25/03/2015	1974 to 2015 Week 12
PubMed	25/03/2015	n/a
JournalTOCS	25/03/2015	n/a

Trial sources searched on: 18th November 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: 18th November 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
- 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$.ti,ab.
3	Radiotherapy/
4	limit 3 to yr="1966-1979"
5	neoplasms/rt [Radiotherapy]
6	limit 5 to yr="1966-1979"
7	(low dose rate or low-dose rate).ti,ab.
8	((internal* or interstitial* or intracavit* or contact*) adj4 (radiotherap* or ((radiation or irradiation) adj4 therap$))).ti,ab.
9	((radiotherap* or ((radiation or irradiation) adj4 therap*)) adj4 (endorect* or endocavit* or Intraluminal* or transluminal*)).ti,ab.
10	(endorect* adj4 (applicat* or catheter* or needle)).ti,ab.
11	Papillon.ti,ab.
12	1 or 2 or 4 or 6 or 7 or 8 or 9 or 10 or 11
13	*Rectal Neoplasms/
14	((rect$ or anus or anal) adj4 (cancer$ or neoplasm$ or lesion$ or tumour$
15	*Anus Neoplasms/
16	or/13-15
17	12 and 16
18	animals/ not humans/
19	17 not 18