NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

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

Locally advanced rectal cancer affects the end part of the bowel (rectum) and nearby tissues. Completely removing it using surgery can be difficult or impossible and some people cannot have it or choose not to have it.

In this procedure, an X-ray tube is inserted through the anus and placed in close contact with the cancer. It releases low-energy radiation into the cancer cells (brachytherapy). It may be done by itself or with other types of radiotherapy or chemotherapy. The aim is to kill the cancer cells while causing as little damage to surrounding healthy tissue as possible.

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Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure 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 overview was prepared in February 2019.

Procedure name

- Low energy contact X-ray brachytherapy (the Papillon technique) for locally advanced rectal cancer

Specialist societies

- Association of Coloproctology of Great Britain and Ireland (ACPGBI)
- Royal Society of Medicine- Coloproctology section
- Royal College of Radiologists - Faculty of clinical oncology.

Description of the procedure

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, obstruction, perforation, pain and discharge. Symptoms may also result from of the tumour invading local structures (such as the bladder). Early stages of rectal cancer may be asymptomatic and between 5% and 10% of patients present with locally advanced disease (stage T3b to T4).

Surgery offers the best chance for cure in some patients with locally advanced rectal cancer. In patients who elect not to have surgery, or are not fit enough to have it, local surgical resection combined with systemic or radiation therapies, or both may be given. The aim is to reduce the tumour size, alleviate symptoms and improve quality of life.

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What the procedure involves

Low-energy contact X-ray brachytherapy (CXB; the Papillion technique) for locally advanced inoperable rectal cancer may be given with external beam radiotherapy or chemotherapy or both. Low-energy CXB is usually delivered in a day-patient setting. The patient is given an enema before treatment, to empty the rectum. 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 through the anal sphincter to ascertain the size and position of the tumour. Subsequently, a rigid endorectal treatment applicator is inserted and placed in contact with the tumour. A contact X-ray tube is introduced into the applicator and treatment commences. This X-ray tube emits low-energy X-rays that penetrate tissue by only a few millimetres, minimising damage to deeper tissues.

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.

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Efficacy summary

Clinical complete response

In a randomised controlled trial (RCT) of 88 patients who had low-energy contact X-ray brachytherapy (CXB) and external beam chemoradiation therapy (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% (11/42) 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). In the same study, a clinical response (greater than 50% reduction in the product of 2 perpendicular parameters) 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).[1]

In a case series of 83 elderly patients with comorbidities and rectal cancer not suitable for, or refused, surgery and treated with CXB after radiotherapy (EBCRT/EBRT) for suspected residual disease (less than 3cm, cT2, cT3, more than 54% node positive) a complete clinical response (cCR; defined as complete absence of palpable, endoscopic or radiological evidence of residual tumour) was reported in 64% (53/83) of patients at a median follow-up of 2.5 years. Incomplete (residual) cCR was reported in 36% (30/83) of patients. Of these, 22 patients had subsequent immediate salvage surgery, 8 patients did not have surgery (because of advanced age, co-morbidities and 2 chose not to) but symptoms were controlled. cCR was sustained (organ preserved with no regrowth of tumour) in 87% (46/53) of patients.[2]

In a case series of 200 elderly patients with comorbidities and rectal cancer not suitable for, or refused, surgery and treated with combined CXB and EBCRT (n=183) or CXB alone (n=17), cCR was reported in 72% (144/200) of patients at a median follow-up of 2.7 years. Incomplete (residual) cCR was reported in 28% (56/200) of patients. Of these, 38 patients had immediate salvage surgery and 16 patients did not have surgery (because of advanced age, co-morbidities and 2 chose not to) but symptoms were controlled. cCR was sustained (organ preserved with no residual tumour) in 86% (124/144) of patients.[3]

In a case series of 112 patients with rectal cancer treated with CXB, cCR was reported in 96% (26/27) of patients in group 1 (with T1N0 <3cm, treated with local excision [LE] plus CXB [for tumours at risk of local disease , n=20] or CXB plus EBRT or CRT for tumours at risk of invasion, n=7); in 96% (43/45) of patients in group 2 (with T2 or early T3, N0 <4cm treated with CXB plus CRT or EBRT to avoid surgery and preserve organ) at a median follow-up of 60 months; and in 37% (15/40) of patients in group 3 (with distal locally advanced T3N0-2, treated with CXB plus CRT or EBRT to shrink the tumour and increase the chance of sphincter saving surgery) at a median follow-up of 40 months.[4]

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In a case series of 63 patients who had CXB followed by EBRT and interstitial brachytherapy boost, cCR (no definition provided) was reported in 92% (58/63) of patients at 2-month follow-up[6].

Tumour recurrence

In the RCT of 88 patients who had 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 CXB/EBRT group and in 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 83 patients, tumour recurrence (local regrowth or distant relapse) after initial cCR was reported in 13% (7/53) of patients. Four patients had local regrowth, 2 patients had local regional nodal regrowth and 1 had a distant relapse. All patients with non-metastatic regrowth (n=6) were managed by delayed surgical salvage. The median interval to relapse was 16 months (range 4 to 11.3 months).[2]

In the case series of 200 patients, tumour recurrence (local regrowth) after initial cCR was reported in 11% (16/144) of patients at a median follow-up of 2.7 years. Three had distant metastasis in addition to local regrowth. Ten patients were managed by delayed surgical salvage. Distant relapse was reported in 3% (4/144) of patients. The median interval to relapse was 16 months (range 4 to 11.3 months).[3]

In a case series of 42 elderly high-risk patients with comorbidities and rectal cancer not suitable for, or refused, surgery (T1N0M0, n=7; T2N0/1 M0 <3cm, n=24; T3N0/1M0 >3cm, n=11) treated with CXB with EBCRT without primary surgical resection, there were no local recurrences in patients with radiological stage T1N0. In patients with stage T2N0, local recurrence was 12% (5/42). Two of these patients had metastatic disease, 3 patients had salvage surgery and 2 had abdomino-perineal excisions with clear resection margins. The median time to local recurrence was 12 months (range 4 to 14 months).[5]

In the case series of 112 patients with rectal cancer treated with CXB, local recurrence was reported in 4% (1/27) of patients in group 1 (with T1N0 <3cm, treated with local excision plus CXB or CXB plus EBRT or CRT); 11% (3/45) of patients in group 2 (with T2 or early T3, N0 <4cm, treated with CXB plus CRT or EBRT to avoid surgery and preserve organ) at 5-year follow-up; and in 6% (15/40) of patients in group 3 (with distal locally advanced T3N0-2, treated with CXB plus CRT or EBRT to shrink tumour and increase chance of sphincter saving surgery) at 3-year follow-up.[4]

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In the case series of 63 patients who had 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].

Distant metastasis

In the case series of 83 patients, distant metastasis was reported in 13% (7/83) of patients. This included 1 patient who had a complete cCR, 2 patients in the incomplete cCR group, 2 patients who had immediate salvage surgery for residual disease and 2 patients who had delayed salvage surgery for local regrowth.[2]

In the case series of 200 patients, 9% (17/200) of patients developed distant metastases. Four had lung resections and others had symptomatic palliative care only because they were elderly with comorbidities.[3]

In the case series of 42 patients, 10% (4/42) of patients developed metastatic disease, 2 of these patients had successful metastatectomies and adjuvant chemotherapy.[5]

In the case series of 112 patients, distant metastases was reported in 17% (95% confidence interval [CI] 0.02 to 0.30) of patients in group 2 (with T2 or early T3, N0 <4cm, treated with CXB plus CRT or EBRT to avoid surgery and preserve organ) and 44% (95% CI 8 to 54) of patients in group 3 (with distal locally advanced T3N0-2, treated with CXB plus CRT or EBRT to shrink tumour and increase chance of sphincter saving surgery) at 5-year follow-up.[4]

Disease-free survival (Kaplan–Meier estimates)

In the RCT of 88 patients who had CXB and EBRT (n=45) or EBRT alone (n=43), disease-free survival rates were 53% and 54% respectively, at 10-year follow-up (p=0.99)[1].

In the case series of 200 patients, disease-free survival rates for the whole group were 72% (95% CI 66 to 78) at 2 years, 65% (95% CI 58 to 72) at 3 years and 53% (95% CI 44 to 62) at 5 years.[2]

In the case series of 83 patients, disease-free survival rates for the whole group were 70% (95% CI 60 to 80) at 2 years, 59% (95% CI 47 to 71) at 3 years and 46% (95% CI 31 to 61) at 5 years.[3]

In the case series of 42 patients, disease-free survival after CXB was 86% at a median follow-up of 24 months (range 5 to 54 months).[5]

In the case series of 112 patients, cancer-specific survival was 87% (95% CI 0.76 to 0.98) at 3 years and 76% (95% CI 0.61 to 0.96) at 5 years in group 2 (n=45

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patients with T2 or early T3, N0 <4cm tumours, treated with CXB plus CRT or EBRT to avoid surgery and preserve organ).[4]

Local progression/recurrence-free survival (Kaplan–Meier estimates)

In the case series of 200 patients, local progression/recurrence-free survival rates for the whole group were 74% (95% CI 68 to 80) at 2 years, 66% (95% CI 59 to 73) at 3 years and 52% (95% CI 43 to 61) at 5 years.[3]

In the case series of 42 patients, local recurrence-free survival after CXB was 88% at a median follow-up of 24 months (range 5 to 54 months).[5]

Overall survival (Kaplan–Meier estimates)

In the RCT of 88 patients who had CXB and 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).[1]

In the case series of 200 patients, overall survival rates for the whole group were 88% (95% CI 83 to 93) at 2 years, 82% (95% CI 76 to 88) at 3 years and 64% (95% CI 55 to 73) at 5 years.[3]

In the case series of 42 patients, overall survival after CXB was 88% at a median follow-up of 24 months (range 5 to 54 months).[5]

In the case series of 112 patients, overall survival at 3 years was 64% (95% CI 0.50 to 0.82) in group 2 (with T2 or early T3, N0 <4cm tumours treated with CXB plus CRT or EBRT to avoid surgery and preserve organ) and 84% (95% CI 71 to 99) in group 3 (with distal locally advanced T3N0-2 tumours treated with CXB plus CRT or EBRT to shrink tumour and increase chance of sphincter saving surgery). At 5-year follow-up the overall survival rates were 40% (95% CI 0.26 to 0.62) in group 2 and 72% (95% CI 54 to 95) in group 3.[4]

In the case series of 63 patients who had CXB followed by EBRT and interstitial brachytherapy boost, the overall actuarial survival rate was 64% 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].

Disease status

In the case series of 83 patients, at a median follow-up of 2.5 years, 83% (69/83) of patients were free from cancer (this included 23 patients who had salvage treatment and 46 patients with sustained cCR).[2]

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In the case series of 200 patients, at a median follow-up of 2.7 years, 81% (161/200) of patients were free from cancer (this included 23 patients who had salvage treatment and 46 patients with sustained cCR).[3]

Organ preservation

In the case series of 200 patients, organ preservation with no residual tumour was reported in 62% (124/200) of patients at a median follow-up of 2.7 years.[2]

In the case series of 112 patients, organ preservation with no residual tumour was reported in 96% (26/27) of patients in group 1 (with T1N0 <3cm tumours treated with local excision plus CXB or CXB plus EBRT or CRT); and 89% (40/45) of patients in group 2 (with T2 or early T3, N0 <4cm tumours treated with CXB plus CRT or EBRT to avoid surgery and preserve organ).[4]

Sphincter-saving procedures and colostomy

In the RCT of 88 patients who had CXB and EBRT (n=45) or EBRT alone (n=43) all patients had 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 in 44% (19/43) of patients in the EBRT-alone group (no p values reported). Abdomino-perineal resections were needed in 24% (11/45) of patients in the CXB/EBRT group and in 56% (24/43) of patients in the EBRT-alone group (no p values reported). The actuarial colostomy rates (Kaplan–Meier estimates) were 29% in the CXB/EBRT group and 63% in the EBRT-alone group at 10-year follow-up ($p<0.001$)[1].

Functional outcomes (as assessed by low anterior resection syndrome [LARS] score)

In the case series of 42 patients, the LARS score for patients who had organ preservation showed that 65% of patients retained ‘reasonable to good’ bowel function (LARS score 0 to 20).[5]

Patient satisfaction

In the case series of 42 patients, 92% (39/42) of patients were satisfied with the treatment and resulting bowel function.[5]

Safety summary

Death

Death due to colorectal cancer was reported in 24% (11/45) of patients who had low-energy contact X-ray brachytherapy (CXB) and external beam radiation therapy (EBRT) and 28% (12/43) of patients who had EBRT alone, at 10-year follow-up, in the randomised controlled trial of 88 patients.[1]

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There were no deaths related to CXB in 3 case series of 83, 200 and 42 patients.[1,2,3]

Rectal ulceration

Rectal ulceration (grade 1) after CXB developed in 30% of patients in 2 case series of 83 and 200 patients, most of which healed within 3 to 6 months.[2,3]

Bleeding

Bleeding (grade 1) due to telangiectasia developed in 28% (23/83) and (56/200) of patients in 2 case series. Haemostasis (grade 2) needing argon beam therapy was reported in 6% (5/83) and 10.5% (21/200) of patients in these studies.[1,2]

Bleeding grade 1 to 2 was reported in 33% (14/42) of patients in 1 study.[4] Rectal bleeding (grade 3; managed conservatively) was reported in 1 patient.[5]

Rectal bleeding after radiation (grade 1 to 2; needing plasma argon coagulation in 2 patients) was reported in 26% (7/27) of patients in group 1 (with T1N0 <3cm, treated with local excision plus CXB or CXB plus EBRT or CRT) in the case series of 112 patients.[4]

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

Rectal necrosis

Grade 2 rectal necrosis was reported in 19% (12/63) of patients at a median of 7 months after treatment, in the case series of 63 patients who had CXB followed by EBRT and interstitial brachytherapy boost. Details about the type of grading system for rectal necrosis were not provided. This healed within 3 to 6 months in all patients. Some patients had rectal necrosis that was accompanied by urgency and minor soiling.[6].

Acute radiation proctitis

Acute radiation proctitis (grade 3) after CXB and CRT was reported in 4% (1/27) of patients in group 1 (with T1N0 <3cm, treated with local excision plus CXB or CXB plus EBRT or CRT) in the case series of 112 patients.[4]

Early and late toxicities

Early grade 3 toxicities (including constipation, faecal incontinence, diarrhoea, and painful proctitis that was successfully treated) were reported in 9% (4/45) of patients in group 2 (withT2 or early T3, N0 <4cm tumours treated with CXB plus CRT or EBRT to avoid surgery and preserve organ) in the case series of 112

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patients. Late grade 3 toxicities (including bleeding in 3 patients at 1 to 2 years after plasma argon coagulation; urgency and stool incontinence at 14 months in 1 patient that resolved with local corticoid in 4 months) were reported in 9% (4/45) of patients in group 2.[4]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened).). For this procedure, specialist advisers listed the following anecdotal adverse events: rectovaginal fistula and rectal stenosis. They considered that the following were theoretical adverse events: rectal perforation and rectal fistula.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to low energy contact X-ray brachytherapy (the Papillon technique) for locally advanced rectal cancer. The following databases were searched, covering the period from their start to 21.11.2018: 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.

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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 advanced 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 588 patients from 1 randomised controlled trial and 5 case series.

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

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Table 2 Summary of key efficacy and safety findings on low energy contact X-ray brachytherapy (the Papillon technique) for locally advanced 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)** Radiological stage: T2 (n=22), T3 (n=62), unknown (n=4) Nodal stage: NO (n=37), N1 (n=46), unknown (n=1) Differentiation: well (n=39), moderate (n=42), poor (n=1, unknown (n=6)
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, 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.

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- Partial 50% response – 50% reduction in the product of 2 perpendicular parameters.

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Key efficacy and safety findings

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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	

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Study 2 Myint AS (2018)

Details

Study type	**Case series**
Country	UK (single centre)
Recruitment period	2003-12
Study population and number	n=**83 rectal cancer patients with residual disease (<3cm) after external beam chemoradiation therapy/radiation therapy [EBCRT/EBRT] not suitable for or refused surgery.** Differentiation: well (n=3), moderate (n=58), poor (n=1), not known (n=21). Radiological stage: cT2 (n=28), and cT3 (n=55). Nodal stage: cN0 (n=38), cN1 (n=32), cN2 (n=12), not known (n=1) Metastasis stage, M0 (n=100%) Tumour size: <3cm (n=47), >3cm (n=23), not recorded (n=13)
Age and sex	Median age 72 years (range 36 to 87 years); 70% (58/83) male
Patient selection criteria	Patients with persistent abnormal findings of residual cancer (endoscopically or radiologically, <3cm) after EBCRT/EBRT who were not suitable for surgery or had refused surgery were included. Patients with complete response after EBCRT/EBRT, those with bulkier residual tumour (>3cm) or tumour that involved half of the rectal circumference (poor responders to EBRT), who had high dose rate endoluminal brachytherapy using a rectal applicator (n=46), those with metastatic disease or tumours with regrowth after EBCRT/EBRT treated palliatively (n=86), those with cT1 or cT2 early tumours who had CXB alone (n=17), those with cT1 or cT2/cN0 tumours that were mainly adenomas with cancer <3cm who had CXB before EBCRT/EBRT (n=26) and all other cT1 and cT4 patients (n=6) were excluded. In addition all patients who had CXB boost within 4 weeks of EBCRT/EBRT (n=26) and those with missing data (n=61) were excluded.
Technique	All patients received escalated doses of radiation directly to the tumour site using **contact X-ray brachytherapy (CXB) boost when residual disease (<3cm) was present after (EBCRT/EBRT).** Most patients received an additional total of 90Gy of CXB radiation delivered in 3 fractions over 4 weeks directly on the tumour-[at 0, 14 and 28 days] (using 50kVp Therapax machine from 2003-9, or using Papillon 50 after 2009 on an outpatient basis) . Patients underwent EBCRT/EBRT at their local cancer units. 12 patients had EBRT alone and the rest had EBCRT (45Gy in 25 fractions over 35 days with concurrent chemotherapy). The interval between EBCRT/EBRT and CXB referral was median 39 days. If any abnormalities observed on MRI, patients were referred for immediate salvage surgery if they agreed and were fit for surgery. Static disease that did not change over time was kept under review.
Follow-up	**Median 2.5 years (range 1.2 to 8.3 years)**
Conflict of interest/source of funding	None, study was funded by NHS.

Analysis

Follow-up issues: short follow-up period, but intensive follow-up was done first 2 years (sigmoidoscopy every 3 months, MRI scans 4-6 months, CT at 12, 24 and 36 months).

Study design issues: retrospective data analysis from a prospectively maintained institutional database. Baseline pre-treatment assessment was performed and TNM staging system was determined from MRI findings. An external validator ensured accuracy of data. Main outcome was local regrowth in those who had clinical complete response [cCR] following CXB after ECBRT/EBRT. A significant number of patients with EBCRT/EBRT were assessed at 4-6 weeks (not in line with international wait and watch protocols). Functional data were not assessed.

Study population issues: heterogeneous group of patients, mainly elderly, and 63% (n=55/83) of patients are with more advanced stage (T3) cancer.

Other issues: There may be considerable overlap in the patient populations of study 1 and 2.

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Key efficacy and safety findings

Efficacy

Number of patients analysed: **83**

Clinical complete response 6 months after last CXB dose

	% (n)
cCR*	63.8 (53/83)
Incomplete CR (residual)	36.1 (30/83)^

(*defined as complete absence of palpable, endoscopic or radiological evidence of residual tumour). ^73.3% (22/30) patients had subsequent immediate salvage surgery, 8 patients did not undergo surgery (because of advanced age, co-morbidities and 2 chose not to) but symptoms were controlled.

Clinical factors associated with treatment response

Univariate logistic regression showed that achievement of complete response was not related to the pre-treatment performance status (p=0.62), age (p=0.74), CT stage (p=0.31), nodal status (p=0.10), tumour size (p=0.27), CXB dose (p=0.82) or EBRT modality with or without chemotherapy (p=0.56).

Local regrowth after initial clinical complete response

	% (n)
Sustained cCR	86.7 (46/53)
Local regrowth/distant relapse*	13.2 (7/53)
Local regrowth only	7.5 (4/53)
Local+regional nodal regrowth	3.7 (2/53)
Distant relapse only	1.8 (1/53)

Median interval to relapse was 16 months (range 4 to 11.3 months). *all regrowth patients (n=6) were managed by delayed surgical salvage.

Clinical factors associated with local regrowth

Univariate analysis showed that tumour regrowth was not associated with pre-treatment performance status (p=0.99), age (p=0.69), cT stage (p=0.81), cN stage (p=0.98), original tumour size (p=0.75), treatment modality (p=0.10), or CXB dose (p=0.25).

Distant metastases

13.2% (7/83) of patients developed distant metastases. This included 1 patient who had after a cCR, 2 patients who had after ISS for residual disease, 2 patients who had after DSS for local regrowth and 2 patients in the incomplete cCR group in addition to their local disease developed distant metastasis.

Disease free survival (Kaplan Meier curves)

	% (95% CI)
2 years	70 (60-80)
3 years	59 (47-71)
5 years	46 (31-61)

Disease status: 83% (69/83) of patients were free from cancer at a median follow-up of 2.5 years (this included 23 salvage treatment patients and 46 sustained cCR patients).

Safety

Adverse events

	% (n)
Death related to CXB	0
Death due to other causes	27/83
Rectal ulceration (grade 1) after CXB, healed within 3 to 6 months	30%
Bleeding (grade 1) due to telangiectasia	28 (23/83)
Haemostasis (grade 2) needed argon beam therapy	6 (5/83)
Colostomy to teat gastrointestinal toxicity	0

Abbreviations used: CXB, contact X-ray brachytherapy; cCR, clinical complete response; DSS, delayed salvage surgery; EBCRT, external beam chemoradiation therapy; EBRT, external beam radiation therapy; ISS, immediate salvage surgery.

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Study 3 Myint AS (2017)

Details

Study type	**Case series**
Country	UK (single centre)
Recruitment period	2003-12
Study population and number	n=**200 rectal cancer patients with residual rectal cancer (<3cm) after EBCRT/EBRT not suitable for or refused surgery.** Differentiation: well (n=10), moderate (n=121), poor (n=6), not known (n=63). Radiological stage: cT1 (n=21), cT2 (n=89), and cT3 (n=87), cT4 (n=3). Nodal stage: cN0 (n=125), cN1 (n=56), Cn2 (n=18), not known (n=1) Metastasis stage, M0 (n=100%) Tumour size: <3cm (n=107), >3cm (n=65), not recorded (n=28)
Age and sex	Median age 74 years (range 32 to 94 years); 67% (134/200) male
Patient selection criteria	Patients with residual rectal cancer (histologically proven, moderately well differentiated, stage T1-3, any N stage, <3cm) after EBCRT/EBRT, not suitable for surgery or had refused surgery those with initial CXB for polyp cancer <3cm were included. Patients with bulkier residual tumour (>3cm) or tumour that involved half of the rectal circumference (poor responders to EBRT) who had high dose rate endoluminal brachytherapy using a rectal applicator (n=46), those with metastatic disease or tumours with regrowth after EBCRT/EBRT treated palliatively (n=86), those who had initial excision of tumour by transanal endoscopic microsurgery, transanal resection of the tumour or endoscopic mucosal resection (n=180) and those with missing data (n=61) were excluded.
Technique	All patients received escalated doses of radiation directly to the tumour site using **contact X-ray brachytherapy (CXB) boost when residual disease (<3cm) was present after EBCRT/EBRT**. Treatment was done with the intent of reducing local regrowth to avoid salvage surgery. Most patients received a total of 90Gy of CXB radiation delivered in 3 fractions, every 2 weeks over 4 weeks directly on the tumour-[at 0, 14 and 28 days] (using 50kVp Therapax machine from 1993-2009, or using Papillon 50 after 2009 on an outpatient basis) . Patients underwent EBCRT/EBRT at their local cancer units. 56 patients had EBRT alone and 127 had EBCRT (45Gy in 25 fractions over 5 weeks with concurrent chemotherapy). The interval between EBCRT/EBRT and CXB referral was median 39 days. If any abnormalities observed on MRI, patients were referred for immediate salvage surgery if they agreed and were fit for surgery. Static disease that did not change over time was kept under review.
Follow-up	**Median 2.7 years (range 1.2 to 8.3 years)**
Conflict of interest/source of funding	None, study was funded by NHS.

Analysis

Follow-up issues: short follow-up period, but intensive follow-up was done first 2 years (sigmoidoscopy every 3 months, MRI and CT scans every 4-6 months). All patients on wait and attach policy were reassessed every 6 months after 2 years.

Study design issues: retrospective data analysis from a prospectively maintained institutional database. Baseline pre-treatment assessment was performed and TNM staging system was determined from MRI findings. An external validator ensured accuracy of data. Main outcome was local regrowth in those who had cCR following CXB after ECBRT/EBRT. A significant number of patients with EBCRT/EBRT were assessed at 4-6 weeks (not in line with international wait and watch protocols). Functional data were not assessed.

Study population issues: heterogeneous group of patients, mainly elderly, and patients with more advanced tumours larger than 3 cm had EBRT/EBCRT locally to downsize the tumours. 17 patients with smaller cancers (<3cm) had CXB upfront as they were not suitable for surgery and refused EBRT.

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Other issues: There may be considerable overlap in the patient populations of study 1 and 2.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **200**

Clinical complete response 6 months after last CXB dose

	% (n)
cCR*	72 (144/200)
Incomplete CR (residual tumour)	28 (56/200)^

(*defined as complete absence of palpable, endoscopic or radiological evidence of residual tumour). ^68% (38/56) patients with residual tumour had immediate salvage surgery, 32% (16/56) patients did not undergo surgery (because of advanced age, co-morbidities and 2 chose not to) but symptoms were controlled.

Clinical factors associated with treatment response

Univariate logistic regression showed that achievement of complete response was not related to the pre-treatment performance status (p=0.15), age (p=0.26), CT stage (p=0.20), nodal status (p=0.59), tumour size (p=0.28), CXB dose (p=0.40) or treatment modality (p=0.20).

Local regrowth after initial clinical complete response

	% (n)
Sustained cCR (organ preservation with no residual tumour)	86 (124/144)
Local regrowth only	11 (16/144)*
Distant relapse only	2.7 (4/144)

Median interval to relapse was 16 months (range 4 to 11.3 months). *3 had distant metastasis in addition to local regrowth. 10 patients were managed by delayed surgical salvage.

Clinical factors associated with local regrowth

Univariate analysis showed that tumour regrowth was not associated with pre-treatment performance status (p=0.83), age (p=0.46), cT stage (p=0.90), cN stage (p=0.63), original tumour size (p=0.50), treatment modality (p=0.50), or CXB dose (p=0.20).

Distant metastases

8.5% (17/200) of patients developed distant metastases. 4 had lung resections and others received symptomatic palliative care only as they were elderly with comorbidities.

Disease free survival (Kaplan Meier curves)

	% (95% CI)
2 years	72 (66-78)
3 years	65 (58-72)
5 years	53 (44-62)

Regression analysis showed that performance status (p<0.001), age (p<0.001) and treatment modality (0.002) were significant factors associated with disease free survival.

Local progression/recurrence free survival (Kaplan Meier curves)

	% (95% CI)
2 years	74 (68-80)
3 years	66 (59-73)
5 years	52 (43-61)

Safety

Adverse events

	% (n)
Death related to CXB	0
Rectal ulceration (grade 1) after CXB, healed within 3 to 6 months	30%
Bleeding (grade 1) due to telangiectasia	28 (56/200)
Haemostasis (grade 2) needed argon beam therapy	10.5 (21/200)
Colostomy to teat gastrointestinal toxicity	0

Many patients died from causes unrelated to cancer.

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Overall survival (Kaplan Meier curves)

	% (95% CI)
2 years	88 (83-93)
3 years	82 (76-88)
5 years	64 (55-73)

Disease status: at a median follow-up of 2.7 years

Disease status	% (n)
Disease free*	80.5 (161/200)
Progressive local disease	11 (22/200)
Distant metastases	8.5 (17/200)

*this included 30 immediate salvage and 7 delayed salvage treatment patients.

Organ preservation with no residual tumour was reported in 62% (124/200) patients.

Colostomy free survival
79.4% of (108/136) patients who were alive at the end of our study period were also colostomy-free.

Abbreviations used: CXB, contact X-ray brachytherapy; cCR, clinical complete response; DSS, delayed salvage surgery; EBCRT, external beam chemoradiation therapy; EBRT, external beam radiation therapy; ISS, immediate salvage surgery.

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Study 4 Frin AC (2017)

Details

Study type	**Case series**
Country	France (1 centre)
Recruitment period	2002-14
Study population and number	n=**112 patients with rectal adenocarcinoma treated using contact X-ray brachytherapy (CXB)**
Age and sex	Mean age: T1N0 <3cm -68 years, T2-T3 N0 <4cm- 74 years, T3 N0-2 -66 years >50% male in all 3 groups.
Patient selection criteria	Patients with a rectal adenocarcinoma accessible to digital rectal examination, located in the distal or middle rectum with a lower edge of tumour <10cm from the anal verge, <4 cm or half circumference (classified according to the UICC TNM 7th edition) were included. Patients unable to stand in knee-chest position, or if the tumour bed was not visible after local excision, those with a palliative strategy were excluded.
Technique	EBCRT 50 Gy + CXB 90Gy **Group 1 (n=27): T1N0 tumours <3cm treated with initial local excision,** if pejorative pathology **adjuvant CXB given** (for those with a risk of local residual disease >10%, risk of perirectal lymph node invasion >10%, **n=20**) **or CXB combined with EBRT or CRT** when a risk of metastatic perirectal lymph node invasion >10% (**n=7**) **Group 2 (n=45): T2 or early T3, N0 (<4cm) treated with CXB plus CRT or EBRT** (to achieve organ preservation and avoid surgery) **Group 3 (n=40): distal locally advanced T3N0-2 treated with neoadjuvant CXB +CRT or EBRT** (to shrink tumour and increase chance of sphincter saving surgery) CXB performed until 2009 using Philips RT 50 machine (dose rate 20Gy/min), in 2010 Papillon 50 machine was used (dose rate 18 Gy/min). Total dose for visible tumour was 90 Gy/3 fractions/4 weeks, and 60Gy in 3 fractions after local excision, and 30 Gy when combined with CRT. In groups 2 and 3 higher dose of 100 Gy or more given for resistant tumours> 3cm and targeted to the lower edge of the tumour. EBRT dose 50 Gy/25 fractions/5 weeks, concurrent chemotherapy twice daily on radiation days. CXB given first ad CRT 4 weeks later, in tumours > 3 cm CRT was glen first. In poor patients chemotherapy was omitted. Interstitial brachytherapy using high dose rate was given in few patients after CXB for tumours reaching the anal canal. Surgery: for T1, T2 tumours local excision was done, radical TME proctectomy in all group 3 patients.
Follow-up	**Group 1: median 63 months; group 2: median 60 months; group 3: median 40 months**
Conflict of interest/source of funding	Study funded by a 3 year grant from a national agency. One of the authors is a medical advisor of Ariane Medical systems, UK.

Analysis

Follow-up issues: follow-up 2 months after treatment and every 3 months, first 3 years and 6 months thereafter.

Study design issues: retrospective analysis of data, for group 1 and 2 the rate of organ preservation (no stoma and no rectal persisting tumour) and for group 3 sphincter saving surgery with no stoma were the main endpoints. Tumour response was assessed using digital rectal examination and rigid rectoscopy at each CXB session and at 8 weeks after radiotherapy in group 2 with additional imaging.

Tumour response was classified according RECIST criteria into clinical complete response, partial response, stable or progressive disease. Local recurrence was defined as any local relapse of the tumour after initial local control in group 1 and 3 or after cCR in group 2. Survival was analysed in terms of overall survival, cancer-specific survival and disease free survival. Toxicity was analysed using the CTCAE V4. Bowel function was assessed with MSKCC score: excellent, good, fair and poor.

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Other issues: results were presented according to subgroups.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **112**

	Group 1 (n=27)	**Group 2 (n=45)**	**Group 3 (n=40)***
Tumour type	T1 N0 <3cm	T2-early T3 N0 (<4cm)	Distal locally advanced T3 N0-2
Treatment	Local excision + adjuvant CXB CXB alone (n=20), CXB with CRT/EBRT (n=7)	CXB alone (n=4), CXB+CRT (or EBRT(n=41)	Neoadjuvant CXB +CRT (or EBRT)
Median follow-up		60 months (95% CI 52-109)	40 months (95% CI 30-65)
cCR^	96% (26/27)	96% (43/45)	37% (15/40)
Partial response		4% (2/45)	
APR			18% (7/38)
LAR (with sphincter saving)			82% (31/38)
Local recurrence	3.7 (1/27)	11% (3/45) at 5 years	6% at 3 years
Distant metastases at 5 years		17% (95% CI 0.02-0.30)	44% (95% CI 8-54) 8 patients
Overall survival			
3 years		64% (95% CI 0.50-0.82)	84% (95% CI 71-99)
5 years		40% (95% CI 0.26-0.62)	72% (95% CI 54-95)
Cancer specific survival			
3 years		87% (95% CI 0.76-0.98)	
5 years		76% (95% CI 0.61-0.96)	
Organ preservation	96% (26/27)	89% (40/45)	
Bowel function score (at last follow-up)	Excellent 7 Good 17 Fair 2	Excellent 4 Good 29 Fair 5 Poor 2	Excellent 4 Good 20 Fair 5 Poor 2

*results analysed only in 38 patients.

^Complete response was defined as total disappearance of the tumour on rectoscopy showing a normal mucosa.

Safety

	Group 1 % (n=27)	**Group 2 (n=45)**	**Group 3 (n=40)**
Acute radiation proctitis (grade 3) after CXB and CRT	3.7 (1/27)		
Rectal bleeding (grade 1-2) after CXB 2 treated with plasma argon coagulation	26 (7/27)		
Early grade 3 toxicity treated (constipation, faecal incontinence, diarrhoea, painful proctitis)		9 (4/45)	0
Late grade 3 toxicities (bleeding in 3 treated by plasma argon coagulation; 1 patient with urgency and stool incontinence at 14 months, resolved with local corticoid in 4 months)		9 (4/45)	
Deaths		21 (6 cancer related)	8 (5 cancer related)

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Abbreviations used: APR, abdominoperineal resection; cCR, clinical complete response; CXB, contact X-ray brachytherapy; EBCRT, external beam chemoradiation therapy; EBRT, external beam radiation therapy; LAR, low anterior resection.

Study 5 Dhadda AS (2017)

Details

Study type	**Case series**
Country	UK (single centre)
Recruitment period	2011-15
Study population and number	n=**42 co-morbid elderly high risk patients with rectal cancer unfit for or refused surgery** Treatment reasons: unfit for surgery (ASA grade 3/4, n=27), refused surgery (n=18), comorbidities (n=24) Radiological stage: T1N0M0 (n=7), T2N0/1 M0 (n=24), T3N0/1M0 (n=11) Site in rectum: low (n=31), mid (n=10), high (n=1).
Age and sex	Median 78 years (range 59 to 94 years); 79% (33/42) male
Patient selection criteria	Patients who had biopsy, computed tomography (CT) of chest, MRI of liver/pelvis and endorectal ultrasound and deemed to be either unfit for radical surgery (with T2/3 N0/1 tumours >3cm) or refused it due to the need for a permanent stoma (with T1 Sm3/T2 N0 tumour <3cm) or those with operative risks from radical surgery related to medical co-morbidities, with no local surgical excision either before or after radiotherapy, no adjuvant chemotherapy after radiotherapy were included.
Technique	**Contact radiotherapy (CXB** using Arianne Papillon 50 machine using 50 kV X-rays) **± external beam chemo/radiotherapy (EBCRT)** without primary surgical excision. CXB: topical local anaesthetic was used, shirking fields were not used and fractions were separated using 2 week intervals. Treatment schedule according to tumour stage: T1Sm1/2 N0: CRT alone (110 Gy fractions [30Gy,30Gy, 30Gy, 20Gy]) T1 Sm3/T2 N0 tumour <3cm (invasive carcinomas): initial CXB [90 Gy/3 fractions] followed by EBCRT (45 Gy) to the pelvis to treat involved occult mesorectal nodes. T2/3 N0/1 tumour >3cm (large/advanced tumours): EBCRT was given initially to allow regression before CXB (was confined to mesorectum and did not go beyond S2/3). Reassessed at 8-12 weeks and if good response (<3cm) CXB is given (90Gy/3 fractions). If poor response radical surgery is done in fit patients.
Follow-up	**Median 24 months (range 5 to 54 months)**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: short term but well defined prospective follow-up (6 weeks, 3 monthly flexible sigmoidoscopy and MRI of liver and pelvis and 12 monthly CT of chest, thereafter frequency reduced, with patients having 6 monthly sigmoidoscopies and MRI scans).

Study design issues: small prospective study with clear protocol, functional outcomes were assessed using a validated patient administered Low Anterior Resection Syndrome (LARS) score. Toxicity was graded using Common Toxicity Criteria. Risk for radical surgery was assessed using the American Society of Anaesthesiologists (ASA) grade.

Study population issues: study included well defined group of patients with early stage tumours (cT1, cT2, cT3a).

Other issues: study included 18 operable patients who refused surgery and suitable for local treatment (<3m, T1N0MO, non-invasive, well differentiated non-ulcerative tumours).

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Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 42
Local recurrence free survival after CXB: 88% with a median follow up of 24 months.
There were no local recurrences in patients with radiological stage T1N0. In patients staged T2N0, local recurrence was 12% (5/42). 2 of these patients had metastatic disease, 3 patients were given salvage surgery and 2 had abdomino-perineal excisions with clear resection margins. The median time to local recurrence was 12 months (range 4 to 14 months).
10% (4/42) patients developed metastatic disease, 2 of these patients had successful metastatectomies and received adjuvant chemotherapy.

Disease free survival after CXB: 86% with a median follow up of 24 months.
Overall survival after CXB: 88% with a median follow up of 24 months.
Functional outcomes (LARS score)
The LARS score for patient who were organ preserved revealed that 65% patients retained reasonable to good bowel function (LARS score 0-20).
Satisfaction with treatment: 92% (39/42) patients were satisfied with the treatment and resulting bowel function.</td><td>Adverse events
<table><tr><td></td><td>% (n)</td></tr><tr><td>Mortality related to CXB</td><td>0</td></tr><tr><td>Estimated 30 day mortality if with radical surgery</td><td>12%</td></tr><tr><td>Bleeding (grade 1-2)</td><td>33 (14/42)</td></tr><tr><td>Rectal bleeding (grade 3, treated conservatively)</td><td>(1/42)</td></tr></table></td></tr>
<tr><td colspan="2">Abbreviations used: CXB, contact X-ray brachytherapy; LARS, low anterior resection syndrome.</td></tr>
</table>

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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, N0-N1, M0 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

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Key efficacy and safety findings

Efficacy

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)

	n	%
Overall survival rate	63	64.4
Age		
Patients aged ≤78	46	78
Patients aged >80	17	0
Tumour diameter		
2–2.9 cm	20	82.4
3–3.9 cm	17	72.7
≥4.0	24	41.5
Circumference		
≤33 %	35	74.5
34–50%	24	58.6
50%	4	0
T stage		
T2	40	81.9
T3	22	34.6
Morphology		
Polypoid ulceration	20	85.7
Fungating	34	51.4
Flat/other	9	75

Safety

- 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.

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Validity and generalisability of the studies

- Low energy X-ray brachytherapy (CXB) was mainly used as a boost in combination with EBRT/EBCRT for symptomatic control in patients with locally advanced rectal cancer who are not suitable for salvage surgery or who are fit but refused surgery.
- Published evidence from retrospective studies on the combination of EBRT/EBCRT with CXB showed reduced local regrowth at 2.5 years.
- There may be considerable overlap in the patient populations of some studies included in table 2.
- Studies in table 2 included elderly patients with different tumour characteristics (mixture of early to intermediate and advanced disease: T1, T2 and T3 tumours, <3cm to >3cm). Patient inclusion in the papers was being defined by either their suitability or desire for surgery.
- 3 studies were from the UK.
- No significant adverse events were reported in 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.

Interventional procedures

- Low energy contact X-ray brachytherapy (the Papillon technique) for early stage rectal cancer. NICE interventional procedures guidance 532 (2015). Available from http://www.nice.org.uk/guidance/IPG532

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- Preoperative high dose rate brachytherapy for rectal cancer. NICE interventional procedures guidance 531 (2015). Available from http://www.nice.org.uk/guidance/IPG531

- Transanal total mesorectal excision of the rectum. NICE interventional procedures guidance 514 (2015). Available from http://www.nice.org.uk/guidance/IPG514

Technology appraisals

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

NICE guidelines

- Colorectal cancer: The diagnosis and management of colorectal cancer. NICE clinical guideline 131 (2014). Available from http://www.nice.org.uk/guidance/CG131
- Colorectal cancer prevention: colonoscopic surveillance in adults with ulcerative colitis, Crohn's disease or adenomas. NICE clinical guideline 118 (2011). Available from http://www.nice.org.uk/guidance/CG118

Cancer Service Guidance

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

Other NICE outputs

- ColonFlag for identifying people at risk of colorectal cancer (2018) NICE Medtech innovation briefing 142
- Colorectal cancer NICE pathway
- Colorectal cancer 2012 NICE quality standard 20

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Additional information considered by IPAC

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. Two Specialist Advisor Questionnaires for low energy contact X-ray brachytherapy (the Papillon technique) for locally advanced rectal cancer were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

No ongoing trials were identified in clinical trial databases.

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3. Sun Myint A., Smith FM et al (2017). Dose escalation using contact X-ray brachytherapy (Papillon) for rectal cancer: does it improve the chance of organ preservation? British Journal of Radiology (90) 1080 20170175 Dec 2017.
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5. Dhadda AS, Martin A, Killeen S, Hunter IA. Organ preservation using contact radiotherapy for early rectal cancer: outcomes of patients treated at a single centre in the UK. Clin Oncol 2017; 29: 198–204.
6. Gerard JP, Chapet O, Ramaioli A et al. (2002) Long-term control of T2-T3 rectal adenocarcinoma with radiotherapy alone. International Journal of Radiation Oncology, Biology, Physics. 54(1):142-9

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Additional relevant papers

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
Dunstan MA, Rockall, TA et al (2018). Radiological and clinical findings following rectal contact X-ray brachytherapy (Papillon technique) – how to assess response. Journal of Contemporary Brachytherapy (10) 2 179-189.	Case series N=7 patients with T2 to 3C N0 rectal adenocarcinoma wished to avoid a stoma or were high-risk for a major operation. Treatments included transanal excision, adjuvant or neoadjuvant chemo/radiotherapy, and Papillon radiotherapy.	Endoscopic and imaging findings following Papillon radiotherapy show that the "black spider" sign of maturing, low signal fibrosis was found to be reassuring, as was the presence of a flat scar on endoscopy. Residual tumor mass or intermediate signal suggest equivocal response, which may necessitate transanal excision. Loss of low signal fibrosis, or the development of soft tissue nodularity or mass should prompt biopsy.	Larger and more relevant studies included in table 2.
Gerard JP, Romestaing P et al (2003). Radiotherapy alone in the curative treatment of rectal carcinoma. The Lancet Oncology, vol 4 (3), 158-166.	Review	T1N0 tumours treated by contact radiotherapy, achieved local control in 85-90% of patients with no severe toxic effects. Combined endocavitary irradiation and external-beam irradiation achieved local control in 80% of patients with T2 tumours and 60% of patients with T3 tumours with only moderate toxic effects and a 60% 5-year overall survival. Radiotherapy alone is suitable for patients with T1N0 lesions (contact radiotherapy) or patients with T2-3 (combined endocavitary and external-beam radiotherapy) who cannot undergo surgery. For T2 or early T3 tumours of the lower rectum requiring surgery and a permanent colostomy, combined irradiation can be used as a first-line treatment to avoid abdominoperineal amputation.	Review
Gerard JP, Myint AS et al (2011). Renaissance of contact x-ray therapy for treating rectal cancer Expert Rev.	Review	Contact x-ray therapy (CXRT) with 50 kV has proven to be an efficient radiation therapy technique to achieve local control and rectal preservation	Review

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Med. Devices 8(4), 483–492.		for early rectal adenocarcinoma. An international collaborative trial (Contact Endoscopic Microsurgery [CONTEM]) was set up to accrue approximately 300 cases of rectal adenocarcinoma staged T1, T2 or early T3 tumors in the UK, France, Denmark and Sweden. This trial should confirm the role of CXRT in curative treatment with organ preservation for early rectal cancers.	
Myint AS (2013). Contact radiotherapy for elderly patients with early low rectal cancers. British Journal of Hospital Medicine (74) 7 391-6.	Review	Many elderly patients with early rectal cancer would like to avoid surgery. Contact radiotherapy should be considered for these patients. Multi-modality treatment should be considered for more advanced tumours (T1/T2/T3/N0M0 >3cms). Contact radiotherapy boost may be given as a palliative treatment in patients with metastatic disease.	Review

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Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	21/11/2018	Issue 11 of 12, November 2018
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane)	21/11/2018	Issue 11 of 12, November 2018
HTA database (CRD website)	21/11/2018	n/a
MEDLINE (Ovid)	21/11/2018	1946 to November 20, 2018
MEDLINE In-Process (Ovid) & MEDLINE Epubs ahead of print (Ovid)	21/11/2018	November 20, 2018
EMBASE (Ovid)	21/11/2018	1974 to 2018 Week 47
BLIC (British Library)	21/11/2018	n/a

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- 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 Radiotherapy/

4 limit 3 to yr="1966-1979"

5 neoplasms/rt [Radiotherapy]

6 limit 5 to yr="1966-1979"

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7	(low dose rate or low-dose rate or "low energy" or "low-energy").tw.
8	((internal* or interstitial* or intracavit* or contact*) adj4 (radiotherap* or ((radiation or irradiation) adj4 therap*))).tw.
9	((radiotherap* or ((radiation or irradiation) adj4 therap*)) adj4 (endorect* or endocavit* or Intraluminal* or transluminal*)).tw.
10	(endorect* adj4 (applicat* or catheter* or needle)).tw.
11	Papillon.tw.
12	CXB.tw.
13	1 or 2 or 4 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	*Rectal Neoplasms/
15	((rect* or anus or anal) adj4 (cancer* or neoplasm* or lesion* or tumour* or tumor* or malignan* or carcinoma* or adenocarcinoma*)).tw.
16	*Anus Neoplasms/
17	or/14-16
18	13 and 17
19	animals/ not humans/
20	18 not 19
21	limit 20 to english language

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