Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

- Determine the quantity of evidence available for a technology of interest.
- Identify any gaps in the evidence.
- Inform decisions on topics that warrant fuller assessment by Health Technology Wales (HTW).

Topic exploration report number:	TER419
Topic:	Low energy contact X-ray brachytherapy (CXB; the Papillon technique) for treatment of early stage rectal cancer
Summary of findings:	The National Institute for Health and Care Excellence (NICE) Interventional procedures guidance (IPG532; 2015) considered low-energy contact X-ray brachytherapy (CXB; the Papillon technique) for early stage rectal cancer. The evidence was adequate to support the use of the technology in patients for whom surgery was not considered suitable (provided that normal arrangements were in place for clinical governance, consent and audit). In patients for whom surgery was considered suitable, NICE stipulated that the procedure should only be used with special arrangements for clinical governance, consent and audit or research due to inadequate efficacy evidence. Further recommendations were made should a clinician wish to use the technology in patients suitable for surgery, but who choose not to have an operation. This topic exploration report focusses on evidence published since NICE IPG532. HTW researchers identified one phase III randomised controlled trial (RCT; OPERA; Gerard et al. 2022) and one large cohort study (CONTEM1; Dhadda et al. 2021). A further retrospective analysis (Frin et al. 2017) was also identified, along with dose-escalation studies (Garant et al. 2019; Sun Myint et al. 2018; Sun Myint et al. 2017). Preliminary results from a phase III RCT and a large cohort study suggest that CXB may be beneficial in the treatment of early stage rectal cancer in patients who are unsuitable for (or chose not to have) radical surgery. Increased organ preservation and favourable rates of local recurrence and survival have been reported. However, these results are only available as conference proceedings and this would limit their value within an appraisal. Economic evaluations indicate that CXB for the treatment of rectal cancer may be cost-effective and affordable for the NHS.

Introduction and aims

Rectal cancer is a common form of bowel cancer, and the introduction of national screening programmes has resulted in an increase in the number of early rectal cancers being diagnosed. Early stage rectal cancer may be classified as T1 (tumour invaded muscularis mucosa; superficial muscle), T2 (tumour invaded muscularis propria; deep muscle) or early T3 (tumour invaded muscularis propria into perirectal fat). Locally advanced T3, T4a and T4b tumours are outside of the scope of this topic exploration.

Surgery is the main treatment for patients with rectal cancer who are treated with curative intent. However, surgery presents risks in terms of long term morbidity and also elevated mortality in an older co-morbid population. In some patients, radiotherapy and/or chemotherapy are used before, during or after surgery to decrease the chances of local recurrence and metastatic disease. There is increasing interest in organ preservation or non-operative management (NOM) of rectal cancer.

Low-energy contact X-ray brachytherapy (CXB; the Papillon technique) aims to improve local control of, or cure, rectal cancer. The procedure is usually performed in a day care setting and involves inserting an X-ray tube through the anus, placing it in close contact with the tumour. The tube emits low-energy X-rays that only penetrate a few millimetres, minimising damage to deeper tissues that are not involved in the cancer. The technology may be combined with neoadjuvant chemoradiotherapy (nCRT).

Health Technology Wales researchers searched for evidence on the clinical and cost-effectiveness of CXB for treatment of early stage rectal cancer.

Evidence overview

Technology assessments and guidelines

NICE Interventional procedures guidance (IPG532; 2015) considered low-energy contact X-ray brachytherapy (CXB; the Papillon technique) for early stage rectal cancer. The evidence was adequate to support the use of the technology in patients for whom surgery was not considered suitable (provided that normal arrangements were in place for clinical governance, consent and audit). In patients for whom surgery was considered suitable, NICE stipulated that the procedure should only be used with special arrangements for clinical governance, consent and audit or research due to inadequate efficacy evidence. NICE recommend that clinicians wishing to use the technology in patients for whom surgery is considered suitable, but who choose not to have an operation, should inform the clinical governance leads. They should also ensure that patients and their carers understand the alternative options for treatment and the uncertainty about the efficacy of CXB, providing clear written information. NICE encouraged further research into use of the technology for early stage rectal cancer.

Systematic reviews and meta-analyses

HTW researchers did not identify any systematic reviews or meta-analyses since NICE IPG352 within the scope of this topic exploration.

Primary evidence

HTW researchers identified one phase III RCT (OPERA; Gerard et al. 2022) and one large cohort study (CONTEM1; Dhadda et al. 2021). A further retrospective analysis (Frin et al. 2017) was also identified,

along with three dose-escalation studies (Garant et al. 2019; Sun Myint et al. 2018; Sun Myint et al. 2017).

Three-year results of the phase III RCT (OPERA; Gerard et al. 2022) have been published as an abstract and were presented as a poster at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting. A total of 144 patients were included in the multicentre (France: 96, UK: 44, Switzerland: 4) study in early T2-T3ab rectal adenocarcinoma. Patients in the experimental arm (Arm B) received nCRT plus CXB boost. Those in Arm B1 had a tumour <3cm and received the CXB boost ahead of nCRT, as compared to those in Arm B2 who had a tumour ≥3cm and received nCRT first. Patients in the control arm (Arm A) received nCRT plus external beam radiotherapy (EBRT) boost. The three-year organ preservation rate (Kaplan Meier estimate) was significantly higher for those receiving the CXB boost (Arm B: 81% vs Arm A: 60%; hazard ratio [HR]: 0.34 [95% confidence interval [CI; 0.19–0.73]; p= 0.005), including for those with a tumour <3cm (Arm B1: 97% vs Arm A1: 65%; HR: 0.081 [95% CI 0.01-0.64]; p= 0.02). The poster presented at the 2022 ASCO Annual Meeting stated that CXB boost combined with nCRT for cT2-T3 <5cm significantly increased the rate of clinical complete response (cCR; 92% vs 64%). There was reportedly no difference in toxicity between the two arms, and good bowel function was preserved in 80% of patients with no difference between the arms. It is unclear when publication of the full results of the OPERA trial are expected.

A large multi-centre cohort study (CONTEM1; Dhadda et al. 2021) investigated CXB in rectal cancer patients with T1 (74%) or T2/T3 (26%) tumours treated with local excision. CXB alone was given in 24 patients, and it preceded or followed external bean chemo/radiotherapy in 170 patients. At a median follow up time of 77 months, local relapse rate was 8% and distant metastases 9%. It was reported that organ preservation was achieved in 95% of patients. Six year local recurrence free and overall survival were 91% and 81% respectively, with cancer specific survival at 97%. No treatment related mortality was observed. The authors noted that long term follow up is required due to unusual late local recurrence.

Frin et al. (2017) presented a single-centre retrospective analysis of 112 rectal cancer patients with T1, T2/early T3, and locally advanced tumours who were given CXB. Group 1 (Tis [in situ]: 3, T1: 21, T2: 3) received local excision followed by CXB alone (20 patients) or CXB and CRT (7 patients). Organ preservation was achieved in 96% of these patients, with only one local recurrence. Group 2 (T1: 2; T2: 23; T3: 20) were treated with CXB alone (4 patients), or CXB plus CRT or EBRT (41 patients). A cCR was observed in 96% of patients and three patients developed a local recurrence (11% at 5 years). The authors reported specific survival was 76% at 5 years and the rate of organ preservation was 89%, with good bowel function in 36 patients. Group 3 consisted of patients with locally advanced tumours, which is outside of the scope of this topic exploration.

Results from the dose-escalation studies (Garant et al. 2019; Sun Myint et al. 2018; Sun Myint et al. 2017) identified were in line with the aforementioned studies and appear to support the use of CXB as an alternative to radical surgery, with favourable rates of organ preservation.

Economic evidence

HTW researchers identified two economic evaluations since NICE IPG532. Neither evaluations were carried out specifically in patients with early stage rectal cancer. However, results may be useful in the consideration of this narrower patient population, as long as there is consideration of potential differences.

Rao et al. (2018a) reported decision analytical modelling and a Markov simulation that compared long-term costs, quality-adjusted life years (QALYs) and cost-effectiveness from the NHS perspective for treatment strategies after CRT. These consisted of watch and wait with CXB when a cCR was not initially achieved after EBRT (WW_{CXB}), watch and wait with EBRT alone (WW_{EBRT}) and

radical surgery. The authors reported that in most scenarios and demographic cohorts, WW_{CXB} had a higher QALY payoff than both WW_{EBRT} and radical surgery. In all plausible scenarios, WW_{CXB} was the most cost-effective, at a threshold of £20,000/QALY. This finding was insensitive to uncertainty associated with model parameters. It should be noted that values may have been different in the narrower population of patients with early rectal cancer that is under consideration in this topic exploration.

Decision analytical modelling with Monte Carlo simulation was used by Rao et al. (2018b) to evaluate long-term costs from the NHS perspective for WW_{CXB}. It was estimated that 818 patients per year are eligible for WW_{CXB} in England and Wales. WW_{CXB} is less costly than standard surgical management for each patient, therefore the more that are treated, the more affordable WW_{CXB} becomes. An implementation cost of <£4 million was reported if as few as 125 patients are treated nationally in 15 centres. The authors report that if the average number of patients treated in each centre is 30, the technology could be cost-saving within 5 years. However, this evaluation included patients with more advanced rectal cancer (in addition to the early stage under consideration in this topic exploration). As such, patient numbers specifically for early stage would be lower; hence the affordability would be lower than that reported in the evaluation and it would likely take longer for the technology to be cost-saving.

Ongoing Research

HTW researchers note that only preliminary results for the phase III OPERA trial and the cohort study, CONTEM1, are currently available. It is unclear when final results can be expected.

Areas of uncertainty

Since NICE IPG532, preliminary results from a phase III RCT and a large cohort study suggest that CXB may be beneficial in the treatment of early stage rectal cancer in patients who are unsuitable for (or chose not to have) radical surgery. Increased organ preservation and favourable rates of local recurrence and survival have been reported. However, conference proceedings are not usually considered eligible for the HTW appraisal process and additional detail on this RCT would be needed to support an appraisal. It is unclear when publication is expected.

Economic evaluations indicate that CXB for the treatment of rectal cancer may be cost-effective and affordable for the NHS. However, none of the evaluations were carried out specifically in patients with early stage rectal cancer. Results may be useful in the consideration of this narrower patient population, but cost-effectiveness and affordability for the NHS may be lower in this group.

Classification of rectal cancer is complex and it is unclear whether some studies have been carried out in patients with early stage rectal cancer. The T3 class may include both early stage and locally advanced rectal cancer, the latter being outside of the scope of this topic exploration.

Literature search results

Health technology assessments and guidance

NICE. (2020). Colorectal cancer. NICE Guideline (NG151). National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ng151 [Accessed 13 Sep 22].

NICE. (2015). Low-energy contact X-ray brachytherapy (the Papillon technique) for early stage rectal cancer. Interventional procedures guidance (IPG532). National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ipg532 [Accessed 13 Sep 22].

NICE. (2006). Laparoscopic surgery for colorectal cancer. NICE technology appraisal guidance (TA105). National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ta105 [Accessed 13 Sep 22].

Stewart AJ, Van Limbergen EJ, Gerard J-P, et al. (2022) GEC ESTRO ACROP consensus recommendations for contact brachytherapy for rectal cancer. Clinical and Translational Radiation Oncology. 33: 15-22. doi: https://doi.org/10.1016/j.ctro.2021.12.004

Evidence reviews and economic evaluations

Rao C, Smith FM, Martin AP, et al. (2018). A cost-effectiveness analysis of contact X-ray brachytherapy for the treatment of patients with rectal cancer following a partial response to chemoradiotherapy. Clinical Oncology (Royal College of Radiologists). 30(3): 166-177. doi: https://doi.org/10.1016/j.clon.2017.11.015.

Rao C, Stewart A, Martin AP, et al. (2018). Contact X-ray brachytherapy as an adjunct to a watch and wait approach is an affordable alternative to standard surgical management of rectal cancer for patients with a partial clinical response to chemoradiotherapy. Clinical Oncology (Royal College of Radiologists). 30(10): 625-633. doi: https://doi.org/10.1016/j.clon.2018.06.010.

Individual studies

Frin AC, Evesque L, Gal J, et al. (2017). Organ or sphincter preservation for rectal cancer. The role of contact X-ray brachytherapy in a monocentric series of 112 patients. European Journal of Cancer. 72: 124-136. doi: https://doi.org/10.1016/j.ejca.2016.11.007.

Garant A, Magnan S, Devic S, et al. (2019). Image guided adaptive endorectal brachytherapy in the nonoperative management of patients with rectal cancer. International Journal of Radiation, Oncology, Biology, Physics. 105(5): 1005-1011. doi: https://doi.org/10.1016/j.ijrobp.2019.08.042.

Gerard J, Barbet N, Thamphya B, et al. (2021). Surgical Tolerability after Chemoradiotherapy. Preliminary Data of phase III OPERA in rectal cancer. Radiotherapy and oncology. 161: S80-S81. doi: https://doi.org/10.1016/S0167-8140(21)07244-3.

Sun Myint A, Smith FM, Gollins S, et al. (2018). Dose escalation using contact X-ray brachytherapy after external beam radiotherapy as nonsurgical treatment option for rectal cancer: Outcomes from a single-center experience. International Journal of Radiation, Oncology, Biology, Physics. 100(3): 565-573. doi: https://doi.org/10.1016/j.ijrobp.2017.10.022.

Sun Myint A, Smith FM, Gollins SW, 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. doi: https://doi.org/10.1259%2Fbjr.20170175.

Sun Myint A, Smith F, Whitmarsh K. (2016). Dose escalation with contact x-ray brachytherapy to improve organ preservation in rectal cancer. Radiotherapy and oncology 2016; 119: S132-S133. Available at: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01740557/full [Accessed 13 Sep 22].

Ongoing research

Schlichtemeier S, Doleman B, Lawrence L, et al. (2018). Outcomes of patients with rectal cancer receiving contact x-ray brachytherapy (CXB, the Papillon technique). PROSPERO 2018 CRD42018092928. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018092928 [Accessed 13 Sep 22].

Key evidence supplied by topic proposer
Dhadda A, Sun Myint A, Thamphya B, et al. (2021). A multi-centre analysis of adjuvant contact X-ray brachytherapy (CXB) in rectal cancer patients treated with local excision – Preliminary results of the CONTEM1 study. Radiotherapy and Oncology. 162: 195–201. doi: https://doi.org/10.1016/j.radonc.2021.07.021. Gerard J-P, Barbet N, Pacé-Loscos T, et al. (2022). Contact X-Ray brachytherapy with chemoradiotherapy is improving organ preservation in early cT2-T3 rectal adenocarcinoma. Three-year Results of the phase 3 Randomized OPERA Trial (NCT02505750). Journal of Clinical Oncology. 40: 16 (suppl) 3512-3512. doi: https://doi.org/10.1200/JCO.2022.40.16_suppl.3512.

Date of search:	September 2022
Concepts used:	Adenocarcinoma; colorectal cancer; contact radiotherapy; contact x-ray brachytherapy (CXB); early stage rectal cancer; low-energy; Papillon technique

Proposed research question and evidence selection criteria (if selected)

Proposed research question	Is contact X-ray brachytherapy (CXB; the Papillon technique) clinically and cost-effective for the treatment of early stage rectal cancer

	Included	Excluded
Population	Patients with early stage rectal cancer Early stage defined as: • TIS (carcinoma in situ) • T1 (tumour invaded muscularis mucosa [MM; superficial muscle]), • T2 (tumour invaded muscularis propria [MP; deep muscle]) or • T3 (tumour invaded muscularis propria [MP] into perirectal fat) Note early stage T3 to be included, but locally advanced T3 excluded.	Patients with locally advanced rectal cancer • Locally advanced T3 • T4a: tumour penetrated the surface of the visceral peritoneum, meaning that it has grown through all layers of the colon. • T4b: tumour grown into, or attached to, other organs or structures.
Intervention	Low-energy contact X-ray brachytherapy (CXB; Papillon technique)	High dose rate brachytherapy
Comparison/ comparators	Surgery; Endoscopic resection; Best supportive care (if surgery unsuitable)	
Outcomes	Rate of clinical complete response; Overall actuarial survival rates (Kaplan–Meier estimates); Three year organ preservation without derivative stoma; Recurrence rates; Patient reported outcome measures (avoidance of anxiety and psychological impact of surgery); Adverse events, e.g. bleeding, necrosis, ulceration, incontinence; Mortality; Resource use and costs (e.g. length of hospital stay)	
Study design	Any. Ideally systematic reviews/RCTs; economic	