Clinical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

The Role of Contact X-Ray Brachytherapy in Early Rectal Cancer – Who, when and How?

A. Sun Myint [*†], A. Dhadda [‡], A. Stewart [§], J. Mills [¶], R. Sripadam [*], C. Rao [||], A. Hunter [‡], M. Hershman [**], A. Franklin [§], E. Chadwick [¶], A. Banerjee [¶], T. Rockall [§], D.M. Pritchard [†], J.P. Gerard [††], UK Papillon Team and International Contact Radiotherapy Network (ICONE)

[*] *Papillon Suite, Clatterbridge Cancer Centre, Liverpool, UK*
[†] *Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, UK*
[‡] *Queen's Centre for Oncology and Haematology, Hull, UK*
[§] *St Luke's Cancer Centre, Royal Surrey County Hospital, Guildford, UK*
[¶] *Oncology Department, Nottingham University Hospitals, Nottingham, UK*
[||] *Cumberland Infirmary, Carlisle, UK*
[**] *Prince Charles Hospital, Merthyr Tydfil, UK*
[††] *Centre Antoine-Lacassagne, Nice, France*

Abstract

The National Institute for Health and Care Excellence (NICE) has recommended the use of contact X-ray brachytherapy (CXB) for rectal cancer patients who are not suitable for surgery. At present, patients with early rectal cancer who wish to avoid major surgery and a stoma are not usually offered CXB as an alternative treatment option to surgery. The main reason for this has been a lack of large, randomised trial evidence, hence NICE encouraged provision of this evidence in their recommendation. In 2015, the OPERA (Organ Preservation in Early rectal Adenocarcinoma) trial was set up and the 3-year organ-preservation results were presented at the American Society of Clinical Oncology (ASCO) meeting in Chicago on 4 June 2022. We are now awaiting full publication of the OPERA results. Most rectal cancer patients who are not suitable for surgery are currently offered external beam radiotherapy (EBRT) with or without chemotherapy after the multidisciplinary discussions. Clinical complete response (cCR) rates vary between 20 and 50% after EBRT. Those who achieve cCR usually adopt a 'watch and wait' policy, but patients who have residual disease are often not offered any additional treatment. We hypothesised that dose escalation with a CXB boost could achieve a higher cCR and therefore lead to improved organ-preservation rates. This was the rationale behind the OPERA trial, which randomised patients between standard of care [EBRT with chemotherapy (EBCRT)] followed by an EBRT boost against EBCRT with a CXB boost to evaluate the role of CXB in dose escalation. In 1993, the first CXB centre was established in the UK at Clatterbridge Cancer Centre. There are now four centres offering CXB in the UK and 10 centres in Europe. Patients should be provided with full information during the consent discussion and offered all the treatment options that are available, so that they can share in decision making and be empowered to make treatment decisions of their choice after proper fully informed consent. Randomised trial evidence of the role of dose escalation with CXB from the OPERA trial, when published, will help in consenting patients who are keen to avoid surgery. We hope this review will help to provide some information about who should be offered CXB, when this modality should be offered and how this is delivered.

Key words: Contact X-ray brachytherapy (CXB); early rectal cancer; organ preservation; Papillon

Background

In the last decade, there has been a paradigm shift in the management of early rectal cancer, with the 'watch and wait' strategy gaining interest as it avoids extirpative surgery and a stoma. There has been a realisation of over-treatment of some early low rectal cancers with abdomino-perineal excision of rectum, which was an operation designed for more advanced cancers a century

This paper was presented at the Multimodality Management of Early Rectal Cancer meeting held at the Royal Society of Medicine in London on 1 September 2021.

Author for correspondence: A. Sun Myint, Clatterbridge Cancer Centre, Liverpool, UK.
E-mail address: sun.myint@nhs.net (A. Sun Myint).

https://doi.org/10.1016/j.clon.2022.10.003
0936-6555/

Please cite this article as: Sun Myint A et al., The Role of Contact X-Ray Brachytherapy in Early Rectal Cancer – Who, when and How? Clinical Oncology, https://doi.org/10.1016/j.clon.2022.10.003

Table 1
Comparative outcomes

Study	*n*	Treatment	cCR	Local regrowth	Organ preservation
Habr-Gama *et al.* [2]	183	EBCRT + chemotherapy 45 Gy/25/35 + 9 Gy	49%	31%	28%
Appelt *et al.* [3]	55	EBCRT + HDR (boost) 60 Gy/30/42 + 5 Gy	73%	23%	56%
Renehan *et al.* [4]	129	EBCRT 45 Gy/25/35	NA	38%	NA
Sun Myint *et al.* [5]	200	EBCRT + CXB (boost) 45 Gy/25/35 + 90 Gy	72%	11%	65%

EBCRT, external beam radiotherapy with chemotherapy; HDR, high dose rate; CXB, contact X-ray brachytherapy; cCR, clinical complete response.

ago. For those patients who opt for a watch and watch strategy, the mainstay of treatment begins with external beam radiotherapy (EBRT), as advocated by the São Paulo group. However, even with escalation of the EBRT dose from 45 to 54 Gy and the addition of chemotherapy, the local regrowth rates remain high and fewer than half of patients achieve organ preservation [1] (Table 1). An alternative option is to use dose escalation with contact X-ray brachytherapy (CXB) as a boost after EBRT [5,6]. CXB uses low-energy X-rays targeted directly on the tumour and there is rapid fall off of radiation dose beyond the tumour. Due to its very low energy (50 KVp), the penetration of radiation dose at depth from CXB is limited to the first 10–20 mm (Figure 1). This is the major advantage of CXB compared with other types of dose escalation. Therefore, CXB allows a very high dose of radiation to be applied directly on the tumour with minimal collateral damage to the normal surrounding tissues [5,6].

Although CXB has been around for more than 90 years, it has never been regarded as a standard of care in rectal cancer. The treatment of low-energy X-rays started before the Second World War, with a machine made by the Siemens company from Berlin to treat patients with cervical carcinoma. Many cases of rectal cancer were treated as well [7]. Siemens stopped manufacturing their machine after the Second World War and the Philips company from the Netherlands took over and continued making low-energy RT50 machines for rectal cancer treatment. The Montpellier group took up non-surgical treatment of rectal cancer first in France and established the dose and fractionation regimens that we still use. Thereafter, Professor Papillon started the CXB facility in Lyon in the early 1950s and popularised this technique. Therefore, CXB is also known as 'Papillon', by which we affectionately acknowledge Professor Jean Papillon (1914–1993) for his commitment in promoting CXB. Philips stopped its production of the RT50 machine in the early 1970s and consequently no treatment machines were available for new centres interested in starting this technique. This explains why there were a limited number of centres with a CXB facility. There was, however, a revival of interest in this technique when a British company ArianeTM (Alfreton, Derby, UK) started

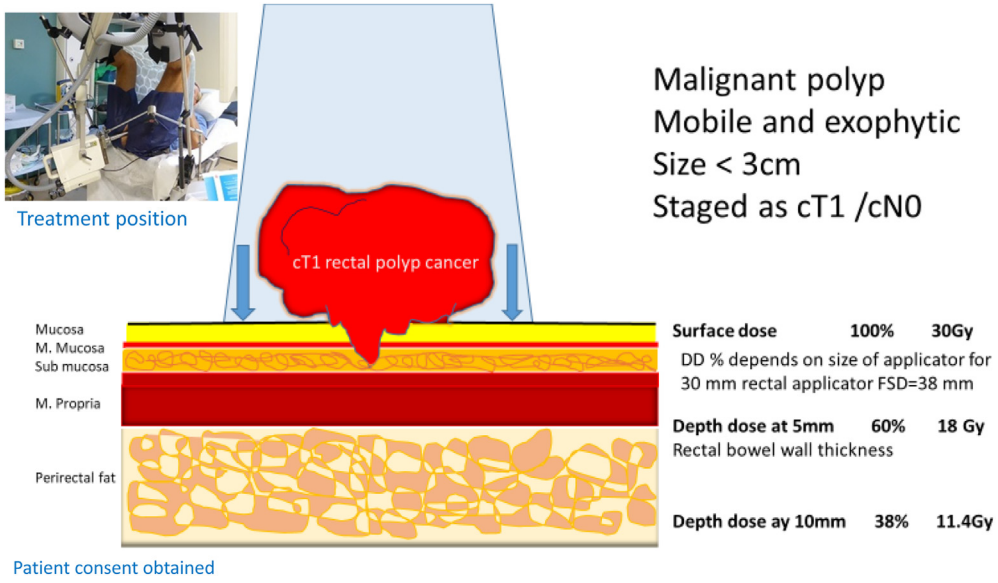

Fig 1. Papillon applicator and treatment set-up.

Please cite this article as: Sun Myint A et al., The Role of Contact X-Ray Brachytherapy in Early Rectal Cancer – Who, when and How? Clinical Oncology, https://doi.org/10.1016/j.clon.2022.10.003

production of Papillon 50© machines [7]. Clatterbridge Cancer Centre received the prototype for its first clinical use in 2008. Over the past 14 years, over 2000 patients have been treated using the Papillon 50 machine, which is the world's largest cohort of patients ever treated by this technique. Our experience at the Clatterbridge Cancer Centre has shown that the clinical complete response (cCR) is higher with early-stage cancers (cT1 or cT2). Local regrowth is seen in 11–13% after achieving cCR [5,6]. In patients who develop local regrowth, those who are fit and agreeable for surgery are able to undergo salvage surgery, with high R0 resection rates [8]. There have been many single institution publications of their experience with CXB, which have shown excellent local tumour control in concordance with our Clatterbridge results [9,10]. The main weakness for adopting this technique has been the lack of large, randomised clinical trial evidence for the efficacy of CXB as a boost after EBRT. We have, however, now completed the recruitment for a phase III randomised trial OPERA (Organ Preservation for Early Rectal Adenocarcinoma) and the results of this trial were presented at the American Society of Clinical Oncology (ASCO) 2022 meeting in Chicago [11]. The data from OPERA will help when consenting patients who are keen to discuss alternative treatment options to avoid surgery and a stoma for their rectal cancer.

Who are the Patients Suitable for Contact X-Ray Brachytherapy?

Patients with early rectal cancer who wish to avoid major surgery and a stoma should be consider for CXB as an alternative treatment option to surgery (Tables 2 and 3). The National Institute for Health and Care Excellence (NICE) has recommended CXB for patients who are not suitable for surgery as a safe and effective alternative to surgery [12]. However, for younger and fit patients who are suitable for surgery, the standard of care is to offer surgery. NICE accepted that there are sufficient data on its safety but advocated a randomised trial to evaluate the efficacy of CXB in this cohort. A multicentre European phase III trial, OPERA, which started in June 2015, has recruited 148 patients, of which 141 were evaluable for analysis. We are now awaiting the publication of the final OPERA trial results, which will provide level 1 evidence for CXB to be considered as the standard of care [11]. Hopefully, this will be a watershed moment and practice changing in the management of early rectal cancer.

Table 2
Indications for contact X-ray brachytherapy treatment

• Patients with histology-proven early rectal adenocarcinoma (endoscopy and biopsy)
• Early-stage rectal tumour confined to bowel wall (cT1/cT2/cN0; magnetic resonance imaging)
• No suspicious lymph nodes (magnetic resonance imaging)
• Mobile exophytic tumour <3 cm in greatest diameter (digital rectal examination and endoscopy)
• Well- to moderately differentiated adenocarcinoma (histology)

Table 3
Indications that patients are not suitable for contact X-ray brachytherapy treatment

• Patients with adverse histological features
• High-grade tumours
• Presence of lymphatic and/or vascular involvement
• Presence of tumour budding
• Mucinous tumours

The Role of Contact X-Ray Brachytherapy in Rectal Cancer

Potential indications for CXB in rectal cancer can be divided into four groups:

(i) Patients with early rectal cancer with an intention for cure (case studies 1 and 2; Figures 2 and 3).
(ii) Patients with early rectal cancer who have had local excision by transanal endoscopic microsurgery (TEMS) or transanal minimally invasive surgery (TAMIS) with an intention for cure.
(iii) Patients with advanced rectal cancer with an intention for cure (case study 3; Figure 4).
(iv) Patients with tumour recurrences or regrowths who are not suitable for surgery with palliative intent (case study 4; Figure 5).

Patients with Early Rectal Cancer with an Intention for Cure (cT1, cT2/cN 0) (Tables 2 and 3).

- Patients with histology-proven early rectal adenocarcinoma (endoscopy and biopsy).
- Tumour stage as either cT1 or cT2 (confine within the bowel wall) [magnetic resonance imaging (MRI) scan]
- Mobile exophytic tumour less than 3 cm in greatest diameter [endoscopy and digital rectal examination].
- Well- to moderately well-differentiated adenocarcinoma (histology).
- No suspicious lymph node involvement (MRI scan).
- Patients suitable and agreeable for long-term follow-up.

It is important to realise that the histological confirmation of adenocarcinoma is not possible in all cases. Malignant-looking polyps on endoscopy with high-grade dysplasia histology or a radiological appearance highly suggestive of malignancy are acceptable to treat with CXB. However, we would advocate local excision to obtain definitive histology before proceeding with CXB whenever possible [13]. If the patient is not suitable for local excision (e.g. not fit for general anaesthesia or refusing surgery),

Please cite this article as: Sun Myint A et al., The Role of Contact X-Ray Brachytherapy in Early Rectal Cancer – Who, when and How? Clinical Oncology, https://doi.org/10.1016/j.clon.2022.10.003

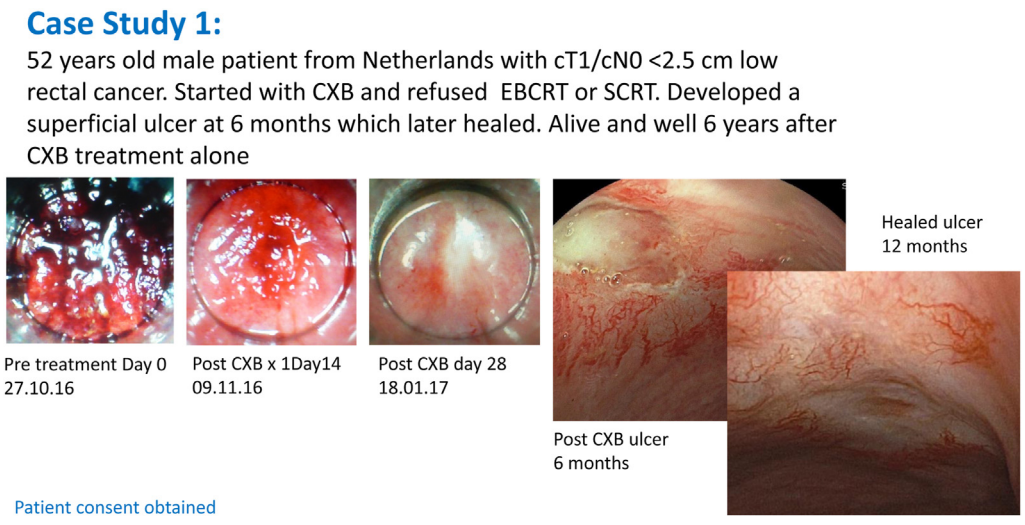

Fig 2. Treatment response – case study 1.

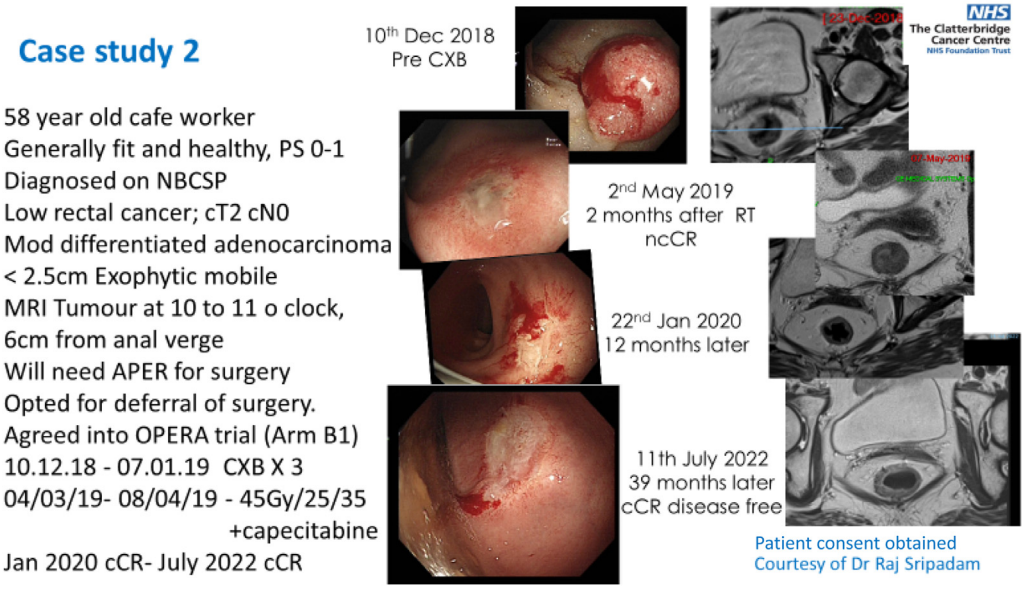

Fig 3. Treatment response – case study 2.

CXB is a safe alternative with agreement from the local colorectal cancer multidisciplinary team (MDT). In addition, tumour staging is not always straightforward, even with high-resolution MRI in experienced hands. We also need to consider endoscopy and digital rectal examination information when interpreting the MRI. Unfortunately, all this information is not always readily available for the reporting radiologist when reviewing the images. Review of all available information is important and there is an urgent need for specialist early rectal cancer MDTs. There should also be a national referral centre to discuss difficult cases.

After initial diagnosis, all patients' cases should be discussed at the local colorectal cancer MDT. In these MDTs, the patients' views are not always forthcoming unless someone who has met the patients previously is present. The decisions made by the MDT are usually based on protocols and guidelines laid down by national bodies such as NICE. These documents do not take into consideration the patient's choice, their needs, their physical and spiritual or religious beliefs. Many patients are prepared to accept less successful oncological outcomes in order to avoid surgery or a stoma [14]. Patients may not know what is best for them, but they certainly know what they cannot cope with, both physically and psychologically. They are the ones who have to live with the consequences of treatment they have received for the rest of their lives [15]. When decisions made by the MDT are relayed to the patient, the clinician in charge of their case should discuss all treatment options that are available and not just discuss what they think is the

Please cite this article as: Sun Myint A et al., The Role of Contact X-Ray Brachytherapy in Early Rectal Cancer – Who, when and How? Clinical Oncology, https://doi.org/10.1016/j.clon.2022.10.003

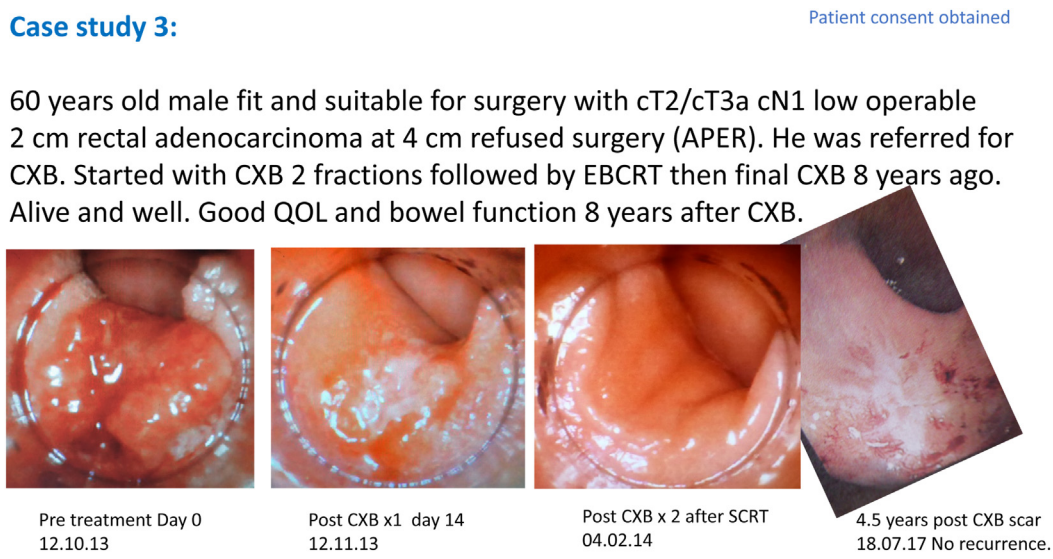

Fig 4. Treatment response – case study 3.

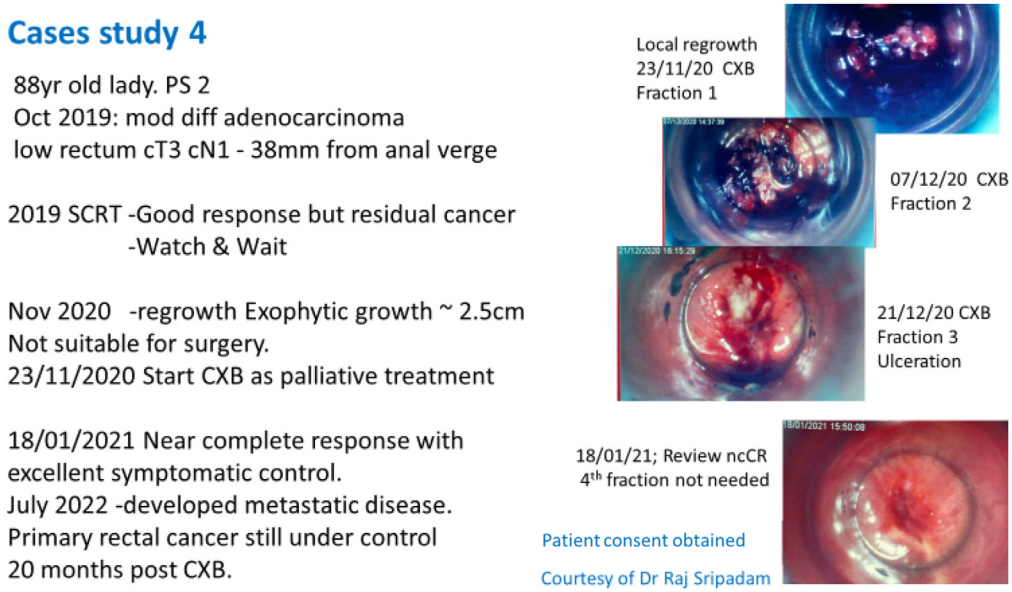

Fig 5. Treatment response – case study 4.

right treatment for the patient. Fortunately, the General Medical Council has now published their recommendations on 'Decision making and consent. Guidance on professional standard and ethics for doctors' [16]. Good practice guidance from the General Medical Council has been modified since the publication of law that changed following the Montgomery case in Lanarkshire [17]. Patients should be given time to reflect on the information provided and also given a chance to discuss matters with their relatives and carers [18]. Their decision should then be conveyed back to the MDT via a colorectal nurse specialist who is the designated key worker looking after the patient's case. Hopefully, in the future, patients will have a choice about what matters most to them, and this will empower the patients to choose what they think is the best treatment that is acceptable for them. What is required is evidence that alternative treatment options are scientifically valid and do no harm to the patients. This much needed valuable data from the randomised trial OPERA will certainly help in future with the consenting process when patients are seeking alternative treatment options to avoid surgery, which is the current standard of care.

The dose given for radical treatment with intent to cure is 90 Gy over 4 weeks. At each fraction, 30 Gy is given as an applied dose with 2 weeks interval in between, allowing time for the normal tissues to recover, while the tumour regresses. Rarely, a fourth fraction is offered if there is a small residual cancer after the third fraction in patients who are not fit for surgery or adamantly refusing surgery, even local excision.

Please cite this article as: Sun Myint A et al., The Role of Contact X-Ray Brachytherapy in Early Rectal Cancer – Who, when and How? Clinical Oncology, https://doi.org/10.1016/j.clon.2022.10.003

Patients with Early Rectal Cancer Who Have Had a Local Excision (pT1/cN0)

Patients with suspicious polyps following endoscopy should be investigated and discussed at an early rectal cancer MDT first before polyp removal. If the suspicious polyps are suitable for local excision, they should have local excision first [13]. If the histology confirms early rectal cancer cT1 cN0 in a patient who had local excision either by TEMS or TAMIS, their case should be reviewed at the early rectal cancer MDT. Those patients who have adverse histological features or evidence of an incomplete resection are usually offered completion surgery. However, if the patient is not suitable for radical surgery or refuses surgery as it involves a stoma, an alternative is to offer them CXB as postoperative treatment and this treatment has acceptable oncological outcomes [13,19]. The target volume should cover the whole scar. The postoperative CXB treatment is usually delivered in conjunction with EBRT as the potential risk of spread of cancer to the lymph node is about 10–20% (depending on the stage of the primary tumour) and the risk of potential spread is not covered by CXB treatment alone, as this is mainly a local treatment [13,19]. The dose given is 60 Gy in two fractions 2 weeks apart, either before or after EBRT, with 4–6 weeks interval in between CXB and EBRT.

Indications for Contact X-Ray Brachytherapy (Postoperative)

- Involved resection margin (R1) or uncertain margin (Rx), especially after a piecemeal removal.
- Polyp with adverse histological features, e.g. poorly differentiated histology, lymphatic or vascular invasion, or both and presence of tumour budding.
- Unexpected pT2 or pT3 histology (should be rare).
- Patients not suitable for completion surgery or refusing surgery.

Patients with Advanced Cancer Who are Either Unsuitable or Refusing Surgery (cT3-cT4/cN1-2)

For patients who are not suitable for surgery or who refuse surgery even though they are fit, the usual practice is to offer patients EBRT either as a short course (SCRT) or a long course with concomitant chemotherapy (EBCRT). The chance of achieving a cCR with EBCRT or SCRT is low and there is generally a need for additional treatment to control the residual cancer [5,6] (case study 3; Figure 4). The dose given is usually 90–110 Gy in 4–6 weeks.

Why Do We Need Additional Contact X-Ray Brachytherapy after External Beam Radiotherapy?

The Brazilian group were one of the first to report the results of a 'watch and wait' policy for rectal cancer. They reported 183 patients who were treated with intensified chemoradiotherapy (54 Gy in 28 fractions over 38 days) followed by four cycles of chemotherapy and achieved a high cCR of 49% [2]. However, 31% of these patients who achieved cCR subsequently developed local regrowth that required surgical salvage with less than 50% chance of achieving organ preservation (Table 1). The chance of a pathological complete response (pCR) after EBCRT for advanced rectal cancer is low, with less than 10% achieving pCR [20]. CXB is not usually suitable for advanced-stage rectal cancer.

Even for early-stage rectal cancer (cT1 an cT2) there is published evidence of residual tumour after either SCRT (TREC trial) or EBCRT (CART trial). Histological evidence of residual cancer could be seen 10 weeks after radiotherapy when TEMS was carried out. The TREC trial from the UK showed 32% pCR 10 weeks after SCRT [21] and similarly the Dutch CARTS study showed 44% pCR following EBCRT [22]. Therefore, there was histological evidence of residual cancer after EBRT even in very early-stage rectal cancer cT1 and cT2 in 68% and 56% of cases, respectively [21,22]. This is the main reason why we need additional treatment to eradicate the residual tumour.

The Danish group constructed a dose–response model to investigate why giving a higher EBRT dose of 60 Gy (usually 45–50 Gy) with an additional 5 Gy brachytherapy boost resulted in 23% local regrowth despite achieving a high cCR rate of 73%. Their model predicted that a minimum of 92 Gy is required to achieve cCR in 50% of cases [3]. It is not possible to deliver 92 Gy even using currently available highly sophisticated latest external beam technology. On the other hand, a CXB boost delivers 90 Gy, which is a very high biological equivalent dose (EQD2) of 300 that is given additional to 45 Gy in 25 fractions over 5 weeks with chemotherapy. This is six times more than the dose administered during standard EBCRT, which obviously is the key to the success of CXB. Moreover, although the additional dose of 90 Gy seems very high, all this high dose is deposited directly into the tumour, with very little dose being administered to the normal surrounding tissues at depth (Figure 1). This is due to the poor penetration of its radiation dose, resulting from its low energy. In practice, we have observed very little toxicity following CXB [5,6,9,10]. The main toxicity is bleeding (grade 1 or 2), which occurs in 40–50% of cases [5,6,9,10]. This is usually due to telangiectasia, which develops 3–6 months after CXB. Bleeding usually settles after 12–18 months. However, in patients who are on anticoagulants and who have persistent bleeding, 10% need argon beam coagulation. Ulceration is another potential toxicity from CXB (Figure 2). This is usually superficial and heals after 6–12 months. NICE has evaluated the toxicity of CXB in detail and regarded this as being acceptable [12].

Patients with Tumour Recurrences or Regrowths Who are Not Suitable for Surgery with Palliative Intent

CXB can also be offered to patients with tumour recurrence after surgery or those who develop local regrowth after EBCRT or SCRT and who are not suitable for surgery or refuse surgery. The dose and fractionation are similar to

Please cite this article as: Sun Myint A et al., The Role of Contact X-Ray Brachytherapy in Early Rectal Cancer – Who, when and How? Clinical Oncology, https://doi.org/10.1016/j.clon.2022.10.003

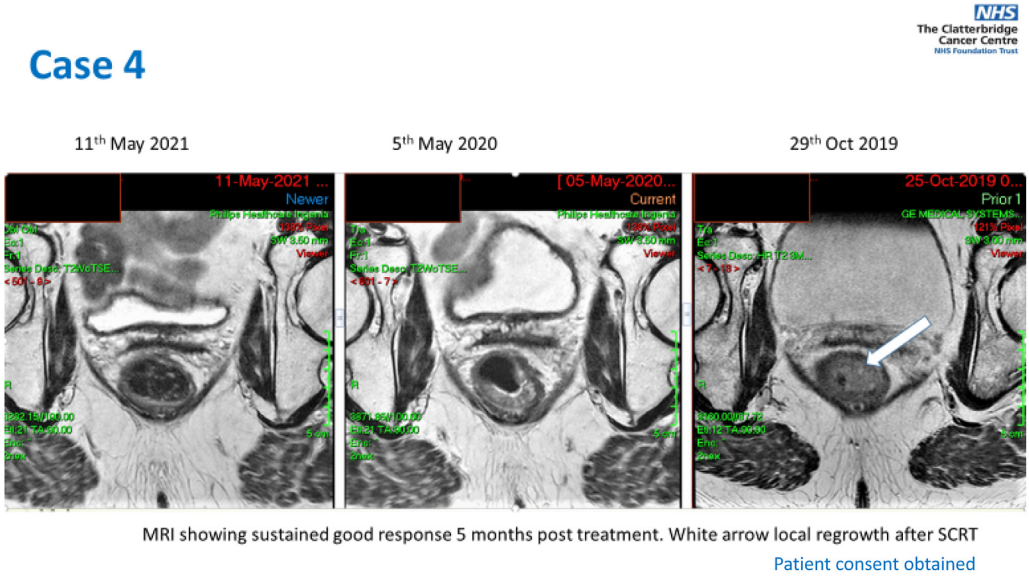

Fig 6. Magnetic resonance imaging response for case study 4.

radical treatment and patients receive 90 Gy in three fractions over 4 weeks (case study 4; Figure 5 showing endoscopic response and Figure 6 showing MRI response).

When Should We Offer Contact X-Ray Brachytherapy?

In general, rectal cancers can be divided broadly into three groups depending on their stage at presentation and their long-term outcomes: the good, the bad and the ugly.

- Good group – patients with early-stage rectal cancer (cT1/cN0) <3 cm can be offered CXB upfront if they are not suitable for surgery or refusing surgery, including local excision. Recently published results of the OPERA trial showed 97% organ preservation with this approach, which is similar to the percentage cure from surgery [11] (case study 1).
- Good group – patients with early-stage rectal cancer (cT1/cN0 or cT2/cN0) >3 cm who are not suitable or refusing surgery should be offered EBCRT or SCRT, first to downsize the tumour to <3 cm, then CXB offered to responders (case study 2).
- Bad group – patients with a more advanced tumour (cT1/cT2/cT3a-b/cN1) of any size should be offered a combination of EBCRT or SCRT followed by surgery. However, in patients not suitable for surgery or refusing surgery, additional treatment with CXB can be offered to improve local tumour control. The sequence of how this is done depends on the size of the original tumour, i.e. <3 cm or >3 cm (case study 3).
- Ugly group – patients with (cT3c-d/any cT4/cN2 and CRM+) should be offered EBCRT first and then surgery. If the patient is not suitable or refusing surgery, CXB can be considered, but only as a palliative treatment, as the chance of local tumour control and cancer cure is very low.

How Do We Offer Contact X-Ray Brachytherapy?

Information on CXB is usually given by the local referring colorectal team when agreement has been reached between the patient and the local colorectal team after a MDT discussion. Patients are usually referred for consideration of CXB when they are not suitable for surgery or when they are refusing surgery, even though they may be fit for surgery. Referral is made to the Papillon centre either by the surgeon or oncologist or colorectal nurse. The cases are then discussed at the weekly Papillon group meeting. If the patients are suitable for CXB, then further information about Papillon and the clinic appointment date is sent out to the patient. This is usually followed by either a telephone or video consultation by the consultant in charge of the case [18].

CXB can be given in an outpatient setting but requires three visits to the nearest Papillon treatment centre. The patient signs the consent document when attending for their first appointment while seeing the oncologist face to face. By then, the patient will have received the information documents about CXB and will have discussed with the oncologist all the treatment options that are available for their rectal cancer. Patient information about CXB is available on the Clatterbridge Cancer Centre website [23] or on the Papillon patients' own information website (papillonpatientsupport.com).

Patients have baseline checks by a radiographer who also administers a microlax© enema to clear the bowel in preparation for their treatment. Treatment can either be administered in the lithotomy position (usually) or prone knee chest (<5%) (Figure 1). Topical lignocaine gel and rectogesic ointment is applied locally around the anus. A rigid sigmoidoscope is then inserted gently to inspect the tumour position, followed by a digital rectal examination. Once the tumour has been located, the treatment applicator size (30, 25 or 20 mm) is selected and inserted depending

Please cite this article as: Sun Myint A et al., The Role of Contact X-Ray Brachytherapy in Early Rectal Cancer – Who, when and How? Clinical Oncology, https://doi.org/10.1016/j.clon.2022.10.003

on the size of the residual tumour. We aim for a treatment margin of 5 mm around the tumour. At first fraction, an applied dose of 30 Gy is delivered straight at the tumour. The surface of the tumour, which is usually raised into the treatment applicator, gets a much higher dose than 30 Gy. It may not be possible to get a clear lateral margin at the start of CXB treatment, but usually after the first fraction most tumours (about 80%) regress and we can get a clear margin before the second fraction in 2 weeks' time. The tumour shrinks in all directions centripetally in most cases. The dose at depth is 60% at 5 mm (Figure 1), which is the thickness of the rectal wall (cT1 and cT2). The third fraction is delivered 4 weeks after the start of treatment. Before the third fraction, there is normally hardly any visible or palpable tumour seen or felt in a responsive tumour (70–80%) (case study 1). Rarely, a fourth fraction of 20 Gy is applied if there is a suspicious small residual tumour (<20%) in patients who are not suitable for salvage surgery or in the small number of patients (<10%) who adamantly refuse any surgery. Anxious patients can have Entonox or equivalent and Valium (5–10 mg) as pre-medication. Most patients do not require any, apart from local anaesthetic.

Assessment after Treatment

The first assessment is carried out at 12 weeks following the last treatment fraction. MRI and endoscopy are usually carried out by the local referring team. It is important that the patient is assessed by the same operator, as the findings are not always easy and are often difficult to interpret. A superficial ulcer can be seen in most cases depending on the size and stage of the original tumour (case study 1). It is important not to biopsy this as the positive predictive value of negative histology is of little clinical use and does not help with the management of the case. This ulcer usually heals in 3–6 months, but can sometimes take longer. If there is local regrowth, an exophytic tumour can be seen arising from the edge of the ulcer. This can easily be seen and felt. A biopsy can then be carried out to establish the diagnosis. In the OPERA trial, 22% of cases had ypT0 histology after surgical salvage and it is important not to rush in with surgery early if there is uncertainty about the local regrowth status [23]. We suggest reviewing the case with endoscopy at 6 weeks and then again at 10–12 weeks after a repeat MRI scan. It is important to note that most local regrowths were detected intraluminal (90%) by endoscopy and not always on the MRI scan [24].

Results

Our experience at Clatterbridge showed that the cCR was higher with early-stage cancers (cT1 or cT2) that are <3 cm and up to 80% of patients remained cancer free at 2.7 years [5,6]. Local regrowth was seen in 11–13% after achieving cCR [5,6]. In patients who developed local regrowth, those who are fit and agreeable for surgery can undergo salvage surgery, with high R0 resection rates [7,25]. The Kaplan–Meier estimates of disease-free survival for the whole group were 72% (95% confidence interval 66–78) at 2 years, 65% (95% confidence interval 58–72) at 3 years and 53% (95% confidence interval 44–62) at 5 years. This reflects that many older patients with medical comorbidities died from non-cancer related deaths. Of the 136 patients who remained alive, 108 (79.4%) were colostomy-free [6]. Our results were in concordance with many other single institution publications of their experiences with CXB [5,6,8–10] (Table 4).

Table 4
Comparative outcomes from international contact X-ray brachytherapy centres

Reference	*N*	Complete clinical response	Local regrowth	Organ preservation
Gerard [11,26]	112	96%	11%	89%
	74	86%	10%	96%
Sun Myint [5,6]	200	72%	11%	62%
	83	64%	11.3%	61%
Dhadda [9]	49	NA	12%	NA
	89	NA	21%	79%
Stewart [27]	105	71%	14%	71%
Van Triest	19	68%	NA	88%
OPERA [11]	69 Arm A	66%	23% Arm A1	63% Arm A1
	72 Arm B	94%	8% Arm B1	97% Arm B1

Follow-up

Most local tumour regrowth occurs in the first 2 years after treatment and this is mainly in the first 12 months [5,6,8,9]. During this period, patients should be followed up closely with regular MRI scans and endoscopies every 3 months in the first year, followed by surveillance at 4 monthly intervals if there is no suspicion of residual disease in the second year. Surveillance is continued 6 monthly in the third year and annually up to 5 years. Published data suggested that the risk of distant metastasis is low in patients who achieved a cCR or near cCR, at less than 8%, and we therefore recommend computed tomography scans of the thorax, abdomen and pelvis at 12 monthly intervals only [6,7,13].

Discussion

There has been a paradigm shift in the management of rectal cancer, especially for early-stage disease over the past decade. There has recently been an increase in the ageing population in Europe, and it is estimated that there will be 60 million people aged 85 years or older in 2033. The UK population mirrors this, with three times the number of older people alive compared with 1988. Surgical mortality and morbidity are higher in older patients, with operative mortality for rectal cancer being more than 15% for 80 years plus patients at 12 months [28]. During the postoperative period, older and more frail patients often need support in

Please cite this article as: Sun Myint A et al., The Role of Contact X-Ray Brachytherapy in Early Rectal Cancer – Who, when and How? Clinical Oncology, https://doi.org/10.1016/j.clon.2022.10.003

high dependency units or even intensive care units for longer than less comorbid and younger patients. Due to poor anal sphincter function, older patients also end up with a higher rate of abdomino-perineal resections, resulting in a permanent stoma. Moreover, there are published data that 32% of Dukes A cancers had abdomino-perineal excision of rectum [29]. In the modern era, with many older patients keen to preserve their quality of life, patients may find that this is not acceptable, and we need to consider an alternative strategy to achieve an equivalent cure rate but with less risk of mortality and morbidity. If the patient is not considered suitable for surgery, EBRT or SCRT is usually offered, but residual tumour is detected in more than 50% of patients even after 10 weeks [20,21]. Most of these patients are not offered any further treatment other than referral to palliative care for symptom control. Unfortunately, many of these patients with early rectal cancer do not develop metastatic disease [5,6,9] and can survive for many years with residual cancer in the rectum causing distressing pain leading to poor mobility, bleeding and foul smelling discharge from the rectum and a poor quality of life. Dose escalation with CXB can increase the chance of higher cCR with lower local regrowth rates. The randomised phase III OPERA trial showed 97% organ preservation for tumours <3 cm when CXB was offered prior to EBCRT [11]. Patients with residual tumour or regrowth after CXB can be salvaged with surgery if they are suitable and agreeable for surgery [7,25]. CXB treatment has been deemed cost-effective and affordable by the National Health Service [30,31]. The downside of CXB is the limited availability of treatment facilities in the UK and Europe, which often require patients to travel long distances if they do not live near the available Papillon centres. The side-effects from CXB are manageable and usually settle down after 12–18 months without the need for surgical intervention. Bleeding is the main side-effect, but only 10% need argon beam to control this. We need more CXB treatment centres in the UK and Europe, so that patients who opt for a non-surgical approach for their rectal cancer can undergo treatment nearer home. Groupe Européen de Curiethérapie European Society for Radiotherapy and Oncology (GEC-ESTRO) has recommended CXB as a boost for patients with early rectal cancer [27]. We therefore need to change the mindset of policy makers to allow an increase in the use of CXB, especially in older comorbid patients with early rectal cancer and also for fit operable patients who are keen to avoid surgery.

Conclusion

CXB can be considered for patients with early rectal cancer who are not suitable for surgery. For those patients refusing surgery, the results from the OPERA trial provide randomised trial evidence to discuss alternative treatment options. The best outcomes can be expected if CXB can be given as an initial treatment for early rectal cancers <3 cm in diameter. For more advanced, larger (>3 cm) rectal cancers in patients who are not suitable or refusing surgery, EBRT either by SCRT or long course, should be considered first to downsize and downstage the tumour, followed by a CXB boost for responders who have a residual tumour <3 cm. Patients with residual tumour or regrowth after CXB can be salvaged with surgery, if they are suitable and agreeable to this approach. We need more CXB centres in the UK and Europe to address the current inequality of service provision for older patients who are not suitable for surgery. Patients should be given full information during the consent discussion and offered all the treatment options that are available, so that they can share in decision making and be empowered to make treatment decisions of their choice after proper fully informed consent. Complex and difficult cases should be referred to centres that have more clinical experience of this technique, so that the patient's chance of cure is not compromised.

Author Contributions

All authors contributed equally towards the manuscript. ASM and RS contributed the figures. ASD and DMP proof-read the article.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Prof Arthur Sun Myint reports was provided by Clatterbridge Cancer Centre NHS Foundation Trust. Prof Arthur Sun Myint reports a relationship with Clatterbridge Cancer Centre NHS Foundation Trust that includes: employment. Prof Arthur Sun Myint has patent pending to None. No conflict of interest to declare

References

[1] Habr-Gama A, Perez RO, Nadalin W, Sabbagh J, Ribeiro U, Silva e Sousa Jr AH, *et al*. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg* 2004;240(4):711–718. https://doi.org/10.1097/01.sla.0000141194.27992.32.

[2] Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, Proscurshim I, Sabbagh C, Lynn PB, *et al*. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. *Int J Radiat Oncol Biol Phys* 2014;88(4):822–828. https://doi.org/10.1016/j.ijrobp.2013.12.012.

[3] Appelt AL, Pløen J, Vogelius IR, Bentzen SM, Jakobsen A. Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. *Int J Radiat Oncol Biol Phys* 2013;85(1):74–80. https://doi.org/10.1016/j.ijrobp.2012.05.017.

[4] Renehan, *et al. Lancet Oncol* 2015;17(2):174–183.

[5] Sun Myint A, Smith F, Gollins S, Wong H, Rao C, Whitmarsh K, *et al*. Dose escalation using contact X-ray brachytherapy (Papillon) for rectal cancer: does it improve the chance of organ preservation? *B J Radiol* 2017;90:2017017. https://doi.org/10.1259/bjr.20170175.

[6] Sun Myint A, Smith FM, Gollins S, Wong H, Rao C, Whitmarsh K, *et al*. Dose escalation using contact X-ray

brachytherapy after external beam radiotherapy as nonsurgical treatment option for rectal cancer: outcomes from a single-center experience. *Int J Radiat Oncol Biol Phys* 2018; 100(3):565–573. https://doi.org/10.1016/j.ijrobp.2017.10.022.

[7] Gérard JP, Dejean C, Montagne L, Benezery K, Doyen J, Hannoun Levi JM. A brief history of contact X-ray brachytherapy 50 kVp. *Cancer/Radiotherapy* 2020;24(3):222–225. https://doi.org/10.1016/j.canrad.2020.01.002.

[8] Hershman MJ, Sun Myint A. Salvage surgery after inadequate combined local treatment for early rectal cancer. *Clin Oncol* 2007;19:720–723.

[9] 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.

[10] Frin AC, Evesque L, Gal J, Benezery K, Francois E, Gugenheim J, *et al*. Organ or sphincter preservation for rectal cancer. The role of contact X-ray brachytherapy in a monocentric series of 112 patients. *Eur J Cancer* 2017;72:124–136.

[11] Gérard JP, Barbet NN, Pacé-Loscos T, Magné N, Serrand J, Mineur L, *et al*. Contact x-ray brachytherapy (Papillon) in addition to chemoradiotherapy to improve organ preservation in early cT2-T3 rectal adenocarcinoma: the 3-year results of OPERA randomized trial (NCT02505750). *J Clin Oncol* 2022: 40. https://doi.org/10.1200/JCO.2022.40.16_suppl.3512.

[12] NICE. Low energy contact X ray brachytherapy (the Papillon technique) for early stage rectal cancer NICE 2015 (IPG 532). Available at: http://nice.org.uk/guidance/ipg532.

[13] Smith FM, Pritchard DM, Wong H, Whitmarsh K, Hershman MJ, Sun Myint A. A cohort study of local excision followed by adjuvant therapy incorporating a contact X-ray brachytherapy boost instead of radical resection in 180 patients with rectal cancer. *Colorectal Dis* 2018;21:663–670.

[14] Gani C, Gani N, Zschaeck S, Eberle F, Schaeffeler N, Hehret T, *et al*. Organ preservation in rectal cancer: the patients' perspective. *Front Oncol* 2019. https://doi.org/10.3389/fonc.2019.00318.

[15] Sun Myint A. Patient choice in the NHS: capturing "decision regret". *BMJ* 2019;366:l5363. https://doi.org/10.1136/bmj.l536.

[16] General Medical Council. *Decision making and consent. Guidance on professional standards and ethics for doctors* November 2020.

[17] Montgomery v Lanarkshire Health Board. *SC* 2015;11(1):1430. AC.

[18] Perkins K, Greenfield L, Whitmarsh K, Sripadam R, Law A, Barnes L, *et al*. Patient information and timing prior to consent for contact X-ray brachytherapy (Papillon): are we doing the process right? *EC Gastroenterol Dig Syst* 2019:757–765.

[19] Dhadda A, Sun Myint A, Thamphya B, Hunter I, Hershman M, Gérard J-P. 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. *Radiother Oncol* 2021;162:196–201. https://doi.org/10.1016/j.radonc.2021.07.021.

[20] The 2017 European Society of Coloproctology (ESCP) Collaborating Group. Evaluating the incidence of pathological complete response in current rectal cancer practice: the barriers to widespread safe deferral of surgery. *Colorectal Dis* 2018;20(suppl. 6):58–68.

[21] Bach SP, Gilbert A, Brock K, Korsgen S, Geh I, Hill J, *et al*. Radical surgery versus organ preservation via short-course radiotherapy followed by transanal endoscopic microsurgery for early-stage rectal cancer (TREC): a randomised, open-label feasibility study. *Lancet* 2021;6(2):92–105. https://doi.org/10.1016/S2468-1253(20)30333-2.

[22] Rutger C, Stijns H, Eelco JR, Nagtegaal ID, Nuyttens JJME, van Meertenet E, *et al*. Long-term oncological and functional outcomes of chemoradiotherapy followed by organ-sparing transanal endoscopic microsurgery for distal rectal cancer the CARTS study. *JAMA Surg* 2019;154(1):47–54. https://doi.org/10.1001/jamasurg.2018.3752.

[23] Patient information on contact X-ray brachytherapy Papillon. Available at: https://www.clatterbridgecc.nhs.uk/application/files/7615/2145/5183/Contact_x-ray_brachytherapy_for_rectal_Cancer-v5_a5.pdf.

[24] van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, *et al*. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet* 2018;391:2537–2545.

[25] Sun Myint A, Thamphya B, Gereard JP. Do non-TME surgery of rectal cancer compromise the chance of cure? Preliminary surgical salvage data from OPERA phase 3 randomised trial. *Clin Oncol* 2021;39(3_suppl). https://doi.org/10.1200/JCO.2021.39.3_suppl.12.

[26] Gérard J-P, Barbet N, Gal J, Dejean C, Evesque L, Doyen J, *et al*. Planned organ preservation for early T2-3 rectal adenocarcinoma: a French, multicentre study. *Eur J Cancer* 2019;108: 1–16. https://doi.org/10.1016/j.ejca.2018.11.022.

[27] Stewart AJ, Van Limbergen EJ, Gerard J-P, Appelt A-L, Verhaegen F, Berbee M, *et al*. GEC ESTRO ACROP consensus recommendations for contact brachytherapy for rectal cancer. *Clin Transl Clin Oncol* 2022;33:15–22.

[28] Morris EJA, Taylor EF, Thomas JD, Quirke P, Finan PJ, Coleman MP, *et al*. Thirty-day postoperative mortality after colorectal cancer surgery in England. *Gut* 2011;60:806–813. https://doi.org/10.1136/gut.2010.232181.

[29] Morris E, Quirke P, Thomas JD, Fairley L, Cottier B, Forman D. Unacceptable variation in abdominoperineal excision rates for rectal cancer: time to intervene? Gut, https://doi.org/10.1136/gut.2007.137877.

[30] Rao C, Smith FM, Martin AP, Dhadda AS, Stewart A, Gollins S, *et al*. A cost-effectiveness analysis of contact X-ray brachytherapy for the treatment of patients with rectal cancer following a partial response to chemoradiotherapy. *Clin Oncol* 2018;30:166–177. https://doi.org/10.1016/j.clon.2017.11.015.

[31] Rao C, Stewart A, Martin AP, Collins B, Pritchard DM, Athanasiou T, *et al*. 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. *Clin Oncol* 2018;30(10):625–633. https://doi.org/10.1016/j.clon.2018.06.010.

Please cite this article as: Sun Myint A et al., The Role of Contact X-Ray Brachytherapy in Early Rectal Cancer – Who, when and How? Clinical Oncology, https://doi.org/10.1016/j.clon.2022.10.003