Supplement article

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# Treatment: the role of contact X-ray brachytherapy (Papillon) in the management of early rectal cancer

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## Introduction

The standard of care for rectal cancer is radical surgery and will remain so for the foreseeable future. Therefore, even for early-stage small rectal cancer, surgery is still regarded as the gold standard of care [1]. However, there is published evidence of the risk of radical surgery in terms of mortality and morbidity, especially for elderly or comorbid patients [2]. In addition, there is an increase in the ageing population in the UK [3]. The majority of rectal cancer patients are above the age of 65 years. Treatment options in an elderly, and often infirm, group require careful consideration to avoid surgical harm. Moreover, many small early rectal cancers are being increasingly diagnosed following introduction of the National Bowel Cancer Screening Programme (NBCSP) which started 10 years ago. The NBCSP has extended its upper age limit to 74 years and many older patients are now included in this programme [4]. They should not be treated for their early screen-detected tumour with extirpative surgery, which was originally designed, over a century ago, to treat more advanced rectal cancers. An alternative treatment option to consider in selected patients with early rectal cancers is contact X-ray brachytherapy (Papillon; CXB) [5]. The National Institute for Health and Care Excellence (NICE) has approved CXB for patients not suitable for surgery [Interventional Procedures Guidance (IPG) 532)].

However, patients who are suitable for, or refusing, surgery must be aware that CXB is not the standard of care.

The CXB procedure can be considered for patients with early rectal cancer not suitable for surgery or in patients who are fit but are refusing surgery because they are stoma phobic.

Situations where use of CXB may be appropriate:

1 Postoperatively;
2 For radical treatment of rectal cancer;
3 As a boost following external beam radiotherapy (EBRT);
4 Palliatively.

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### Postoperative CXB

When an unexpected malignancy is diagnosed following removal of a rectal polyp by endoscopic mucosal resection (EMR), transanal endoscopic microsurgery (TEMS) or transanal minimally invasive surgery (TAMIS), the standard of care generally is to offer patients completion surgery [1]. This has the advantage of providing accurate pathological staging. However, if the patient is unfit for radical surgery or refuses surgery because this involves a permanent stoma, postoperative CXB can be considered alongside EBRT to treat occult nodal disease [6]. The indications for postoperative CXB [7] are as follows:

1 High-risk features in a polyp, including:
   a Poorly differentiated adenocarcinoma (< 10%);
   b Positive extramural venous invasion (EMVI);
   c Tumour budding.
2 Resection margin uncertain (as a result of piecemeal removal) (Rx);
3 Resection margin close (< 1 mm) (R1) or involved (R2);
4 Histology confirmed unexpected pT2 or pT3 (rare).

*Radical CXB alone*

When a small (< 3 cm) early (cT1) rectal adenocarcinoma is diagnosed in a patient unfit for radical surgery or in an elderly patient with multiple comorbidities, radical CXB alone can be considered [5].

Selection criteria for radical curative CXB are:

1 Histologically confirmed rectal adenocarcinoma;
2 Well- to moderately differentiated tumour;
3 Maximum tumour size < 3 cm at the greatest diameter;
4 Mobile exophytic tumour (most suitable);
5 Tumour located within the reach of a rectal treatment applicator (usually < 10 cm);

6 Patient suitable for long-term follow-up.

Exclusion criteria:

1 Poorly differentiated adenocarcinomas (< 10% of cases);
2 Presence of EMVI (EMVI+);
3 Presence of suspicious mesorectal lymph node (caution: not always reliable by MRI assessment).

*Previous pelvis radiotherapy*

In patients who have had radical radiotherapy for previous malignancy (e.g. prostate, bladder, anus or cervix) and develop rectal cancer later as a second malignancy, radical CXB alone can be offered if the patient is not suitable for surgery or refuses surgery because it involves a permanent stoma.

#### CXB as a boost in addition to external beam chemoradiotherapy or external beam radiotherapy

In an early-stage large rectal tumour with size > 3 cm at maximum diameter (cT1) or more advanced stage cancer of any size (cT2), EBRT is usually offered to downsize or downstage the tumour and to address possible lymph node spread, and CXB is considered as a boost either before or after, depending on the size of the tumour (< 3 cm) [5].

The option for CXB boost is only possible in larger tumours (> 3 cm) if there is a good response (more than 60% reduction in size) to initial external beam chemoradiotherapy (EBCRT) or EBRT. The residual tumour must be < 3 cm because the largest applicator size available for CXB is 30 mm. This approach is particularly useful for patients who are not suitable for surgery, older patients who are at high risk for surgery and those who are fit but refusing surgery because they are stoma phobic. If there is residual tumour or regrowth at a later date, salvage surgery can be offered without compromising their chance of cure [8].

#### Palliative CXB

In patients with small anastomotic recurrence following previous radiotherapy (pre- or postoperative) and surgery who are not suitable for further salvage surgery or are refusing surgery, CXB can be offered to control symptoms of bleeding and rectal discharge. CXB can also be offered in patients with inoperable metastatic disease for symptom control of residual primary tumour or recurrence following EBCRT or EBRT [9].

## What is CXB?

Contact X-ray brachytherapy uses low-energy (50 keV) X-rays which are deposited mainly on the surface of the tumour and penetrate only a few millimetres of tissue beneath the tumour. Therefore, exophytic tumours are more suitable for this procedure than deeply infiltrative tumours. CXB treats only a small volume, usually < 5 $cm^3$ of tissue, compared with EBRT which treats much larger volumes of tissue, of about 1000–1500 $cm^3$. Therefore, very high doses of radiation (~30 Gy, but with a biological dose equivalent to 100 Gy) can be safely delivered at each treatment fraction with very little collateral damage to the normal tissues around the tumour. The X-ray beam is targeted, under direct vision, straight onto the tumour with a small margin (usually 5 mm). Tumour is shaved off layer by layer (a few millimetres at a time) every 2 weeks, after which the next treatment is given. During the 2-week interval between treatments, the normal tissues recover and the tumour regresses, usually centripetally [5,10]. At the end of the third treatment, very little residual tumour can be seen or felt in a responsive tumour (Fig. 1). An MRI performed at 12 weeks from start of treatment shows mainly fibrosis with tumour regression grade (TRG) 1 or TRG 2 (Fig. 2).

## How do we perform CXB?

Patients suitable for CXB can be treated as a day case/outpatient. Patients are treated either in lithotomy (Fig. 3) or knee chest (Fig. 4) position, depending on the location of the tumour. The majority of patients do not require general anaesthesia. However, local analgesic (lidocaine gel) is used together with topical glyceryl trinitrate or equivalent to relax the anal sphincter muscles. Rigid sigmoidoscopy is carried out first of all, to identify the tumour site (i.e. the location in the rectal wall) and size. The size of rectal applicator is selected to include the tumour with a 5 mm margin around it. The rectal applicator is inserted gently and the position secured using a clamp to hold the applicator in place during the treatment. The radiation treatment takes just over 1 min but the whole preparation, including positioning, usually takes < 30 min [11]. The treatment is usually well tolerated and patients are able to go home soon afterwards. We have not encountered any readmissions because of active bleeding or pain following CXB treatment.

## Radiation dose and fractionation

The radiation dose and fractionation depends on whether the tumour has been removed surgically first with TEMS or EMR. Two fractions of 30 Gy are given with a 2-week gap (total 60 Gy) for postoperative patients, usually in conjunction with EBRT [7]. For radical CXB in older patients with an early (cT1) small

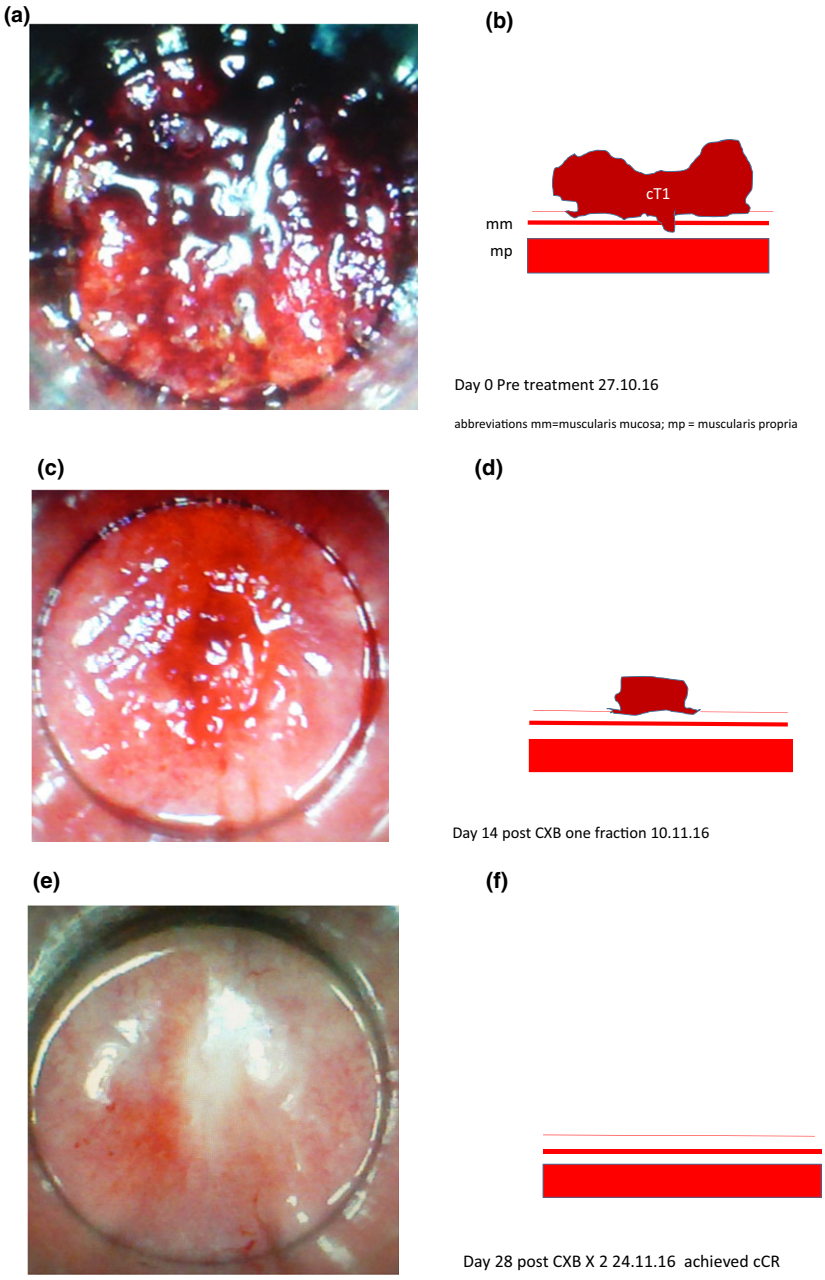


**Figure 1** Response of a 52-year-old man from the Netherlands, with a 20 mm cT1cN0cM0 adenocarcinoma, to contact X-ray brachytherapy (CXB) (Papillon) alone. Endoscopic response: day 0 pretreatment (a); day 14 post CXB first fraction (c); and day 28 post CXB second fraction (e). (b, d, f) Corresponding diagrammatic cross-section responses. A clinical complete response was achieved after the second fraction of CXB (indicating that the tumour was radiobiologically favourable). The patient refused external beam therapy to avoid toxicity and was not offered. The risk of nodal spread predicted was < 5–10% from a cT1 tumour. A close 'watch-and-wait' follow up was adopted, with regular digital rectal examination (DRE), MRI, CT (CAP) scan and endoscopies every 3 months. Twenty-four months after CXB alone, the patient was alive and well with a good quality of life, and had good bowel, sexual and sphincter function.

tumour (< 3 cm) that has not been removed surgically, the total dose usually is 90 Gy in three fractions every 2 weeks with EBRT. Rarely, 110 Gy in four fractions can be offered in patients not suitable for surgery if CXB alone is used [7]. For more advanced-stage tumours (cT2, cT3a) or larger tumors with size >3cm, EBRT or EBCRT is offered first to downsize or down-stage the tumour before CXB [5,7].

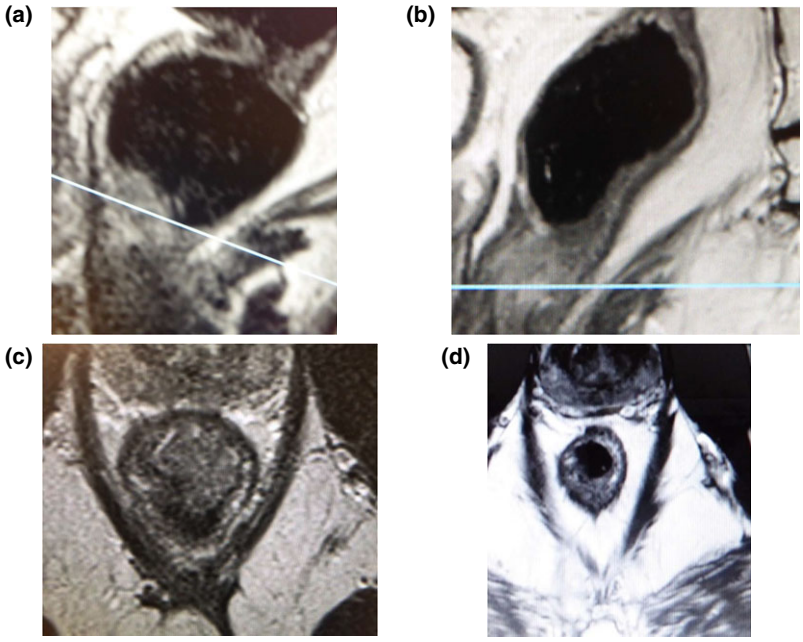


**Figure 2** Magnetic resonance imaging response to contact X-ray brachytherapy for the same patient. (a, c) Anterior tumour in low rectum has regressed completely in corresponding views shown in (b, d).

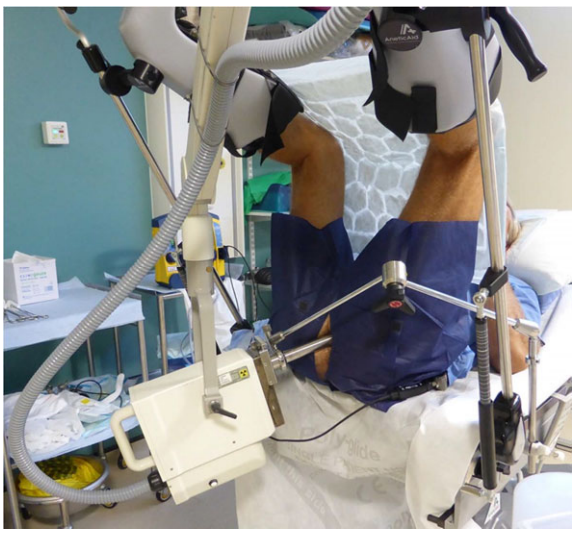

**Figure 3** Treatment in lithotomy (supine) position.

## Response assessment

In patients who are either not suitable for surgery or are refusing surgery, assessment is performed 14 weeks from the start of treatment with either CXB or EBCRT (CXB boost patients are assessed 8–10 weeks after starting EBCRT). If there is significant (more than 80%), but incomplete, clinical response (suspicious of residual disease), it is recommended that further assessment is carried out at 20 weeks and finally at 24 weeks from the start of treatment before making a final decision on continued surveillance or surgery [10]. Triple assessment with digital rectal examination (DRE), endoscopy and high-resolution MRI are carried out [8] (Figs. 1,2).

## Outcomes

There are three possible outcomes:

1 Clinical complete response (cCR): no residual tumour visible on endoscopy (Fig. 1e,f) palpable on DRE or detected on MRI (Fig. 2b,d). No further treatment is necessary and the patient just needs regular close follow up, similar to the 'watch-and-wait' protocol (see below).
2 Small mucosal or palpable abnormality suspicious of residual tumour: consider TEMS or local full-thickness excision in selected cases, if the patient is not keen or fit for extirpative surgery.
3 No response: no regression (very rare) or regression of residual tumour to less than 30% of the original size. Consider salvage surgery if the patient is suitable for surgery and agreeable. Further response from additional CXB is not possible in our experience.

## Follow-up

We adopt a careful watch-and-wait policy for patients who achieve cCR after CXB [5,12]. Regular DRE,

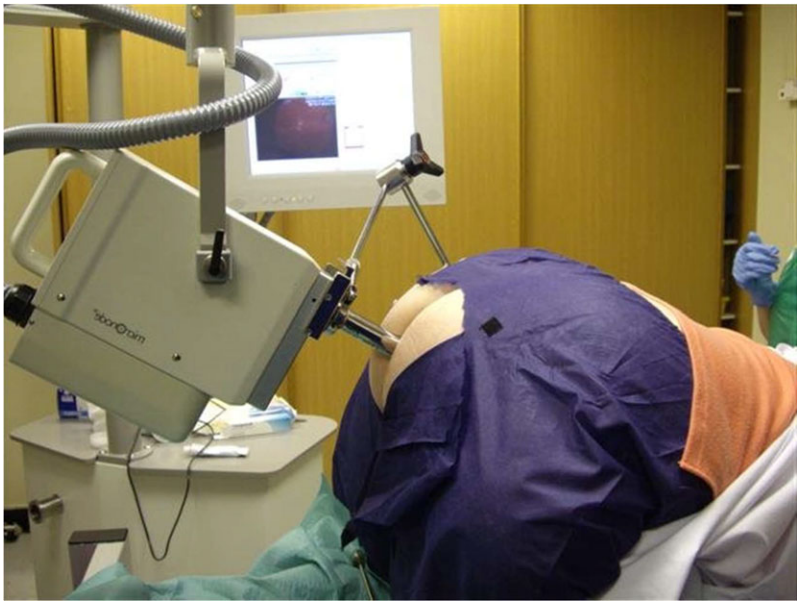

**Figure 4** Treatment in knee chest (prone) position.

endoscopy and MRI are carried out at local referring hospitals alternating with the CXB centres at the following intervals: every 3-4 months in the first 2 years (when the risk of regrowth is highest); at 6-month intervals in the third year; and annually up to the fifth year. No radiological assessment is carried out after 3 years unless there is suspicion of residual tumour present or as per local follow-up policy. Any persistent abnormalities on DRE, endoscopy and/or MRI should be followed up and, if these abnormalities progress, salvage surgery should be considered if the patient is fit and agreeable for such treatment [8,11–13].

## Side-effects from CXB

Persistent ulceration can occur in 30% of patients following CXB. Ulceration is usually superficial; the edges are not raised and no induration is felt at the base (Fig. 5a). This type of post radiation ulcer usually heals within 3–6 months (Fig. 5b) [14]. We do not advise biopsy of this ulcer as the negative histology has very limited predictive value. Also, it can delay ulcer healing as a result of the high-dose radiation to this area from CXB. If there is residual tumour beneath the ulcer, the edges are raised and/or the base of the ulcer is indurated. Subtle abnormality on the mucosa may not be detected by MRI and therefore it is important not to rely solely on the MRI reports but to repeat the endoscopy regularly, with the procedure performed by an experienced observer. If there is uncertainty, continue close observation every 6–8 weeks or seek advice from an experienced centre.

Bleeding can occur within a year after CXB in 28% of patients, and bleeding can persist (G1 or G2) for up

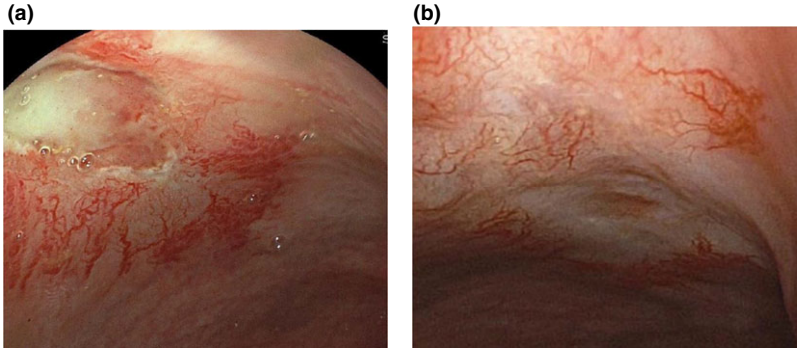


**Figure 5** Post radiation ulcer of the same patient. (a) 12 weeks after contact X-ray brachytherapy. (b) Showing healing after 24 weeks. Healing continues at 36 months.

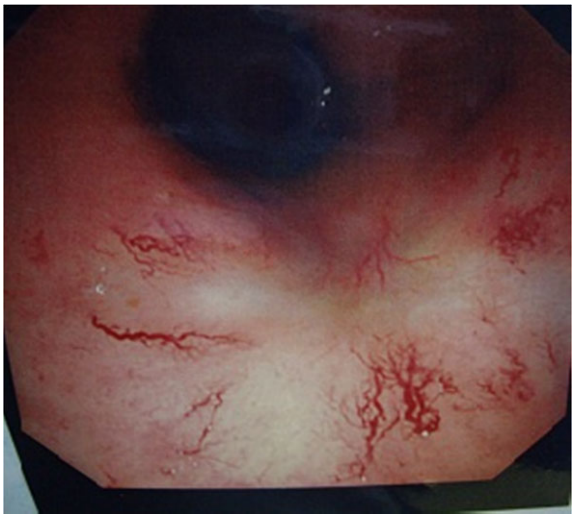

**Figure 6** Telangiectasia (dilated tiny blood vessels caused by the late radiation effect) around the Papillon scar, from where bleeding (G1 or G2) usually occurs in about 30% of patients. This usually settles after 12–18 months but 10% of patients need argon beam therapy (G3) to control the bleeding.

to 2–3 years, especially if the patients are on antiplatelet therapy or anticoagulants. In 10% of patients with severe persistent bleeding (G3) argon plasma coagulation (APC) is required to control bleeding from telangiectasia (dilated small blood vessels caused by late effects of radiation) around the Papillon scar [5,14] (Fig. 6).

No deaths related to CXB have been reported. Pain is not common, but biopsy could aggravate the pain if the tumour is low, near the anorectal junction. NICE has reviewed the side effects of CXB as acceptable and have published their findings as IPG 532 [14].

## Management of local regrowth

Local regrowth following CXB, alone or in combination with EBCRT or EBRT, usually occurs in the first 2 years [5,9]. The local regrowth manifests itself as a mucosal abnormality which gradually progresses and, after some months, exophytic growth can be seen and felt. If there is suspicion of local regrowth, biopsy can then be carried out but may just show high-grade dysplasia as the recurrent tumour is usually situated quite deep and embedded within or beneath the muscle [5,10,12]. If the patient is suitable for surgery and agreeable, they should be offered salvage surgery. CXB is not suitable for local regrowth following EBRT or EBCRT, but could be offered if the patient is not suitable for surgery or refusing it. Regrowths do not respond well to CXB as they are likely to be more radio-resistant (because of unfavourable biology) than the original tumours. Therefore, if there is uncertainty, it is important not to delay referring patients with persistent mucosal abnormalities (suspicious of residual tumour) following EBCRT or EBRT to experienced centres for further assessment within 6 months of the start of EBCRT, especially in patients not suitable for surgery. There are several published reports on successful salvage surgery for local regrowth following CXB after EBCRT [8,12,13]. Unfortunately, not all patients with local regrowth are suitable for, or agree to, surgery and such patients may need referral for supportive palliative care to control symptoms for their residual or recurrent rectal cancer. Patients should be aware that CXB does not cure all rectal cancers.

## Discussion

Contact X-ray brachytherapy has been in clinical use for over 80 years [5]. However, its use is limited to a few centres as there was no replacement for the original Philips machines (Philips, Eindhoven/Amsterdam, the Netherlands) until recently. There is now a revival of interest in CXB as a result of the availability of new British-made machines (Papillon 50 and Papillon plus; Ariane, Alfreton, UK) (Fig. 7). There are now four centres

**Figure 7** Papillon Plus treatment machine (Ariane).

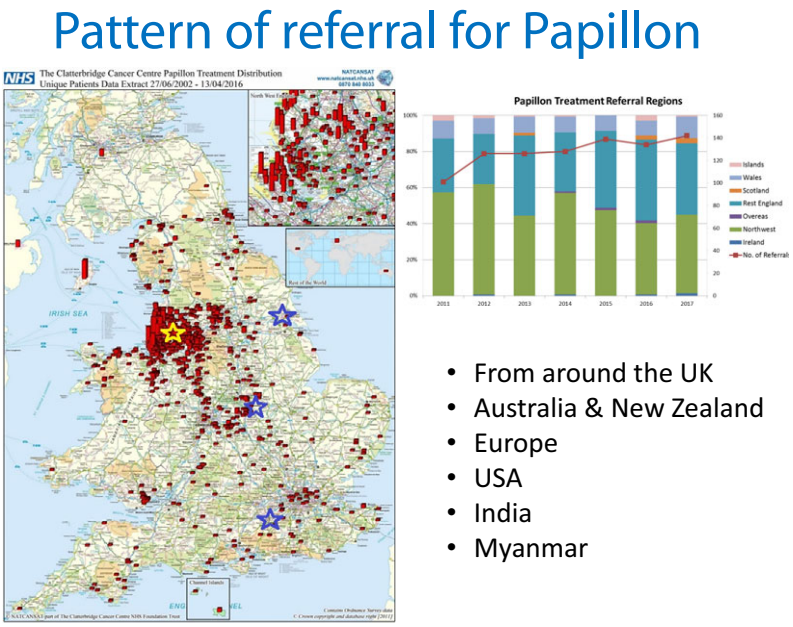


**Figure 8** Map showing referrals to Clatterbridge and UK Papillon centres (stars).

in the UK that can offer CXB (Clatterbridge, opened in 1993; Hull, opened in 2011; Nottingham opened in 2014; and Guildford opened in 2014) (Fig. 8). There are 15 centres situated around Europe. NHS England is reviewing the commissioning of specialist services in the UK to address the inequalities of Papillon service provisions across England (Fig. 8). It is likely that a larger number of CXB facilities will be available in the future, nearer to home for older patients suitable for CXB but with limited mobility. NICE guidelines recommend all potential cases to be discussed by local colorectal multidisciplinary teams (MDTs). Possible treatment options which include surgery (the standard of care), TEMS, EBCRT, EBRT and CXB should be discussed at MDT meetings. Recommendation made by the MDT should be explained to the patient and their carers, after the MDT meeting. If patients and carers opt for nonsurgical treatment (patient's choice), all suitable cases should be referred to the nearest Papillon centre for assessment and treatment, with the aim to reduce the likelihood of a local regrowth [14]. In addition, NICE has recommended a Papillon National Database, which has now been set up at Guildford for audit (2016). To facilitate information on evidence-based research, the International Contact Radiotherapy Network (ICONE) has initiated a Phase III multicentre randomized European trial of Organ Preservation in Early rectal Adenocarcinoma (OPERA). This trial should provide the much-needed randomized evidence for the role of CXB in early rectal cancer [15]. This is one of the 'hard to do trials' but is accruing well at present and we await the outcome with interest.

## Conclusion

Contact X-ray brachytherapy can be offered to patients with early rectal cancer not suitable for surgery. For patients with more advanced rectal cancer who are fit but refuse surgery usually to avoid a stoma, CXB can also be considered for small residual tumour (< 3 cm) after EBCRT or EBRT. As CXB is a highly targeted treatment, there is very little collateral damage to the normal surrounding tissues. In addition, if there is residual tumour after CXB boost following EBCRT, salvage surgery can be considered (if the patient agrees) without compromising chance of cure. Advice should be sought for difficult and complex cases after MDT discussion (for patients not suitable for, or refusing, surgery) from centres with experience regarding alternative treatment options to surgery, in selected cases.

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## Declaration of conflict of interest

None of the authors.

## Achievement

UK Papillon team has won the prestigious BMJ award for 'Cancer Care Team of the Year-2018'.

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## Supporting Information

The video may be found on Clatterbridge Cancer Centre website and also on the Colorectal Disease Journal YouTube and Vimeo channels:

**Video S1.** Patients treatment information and consenting on Papillon. https://www.clatterbridgecc.nhs.uk/patients/treatment-and-support/papillon

**Video S2.** Information to the professional on Papillon. https://www.clatterbridgecc.nhs.uk/professionals/education-and-courses/papillon-training-course