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Role of radiotherapy in the treatment of rectal cancer in older patients

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ABSTRACT

Striking a balance between cancer treatment and patient-centred care is becoming ever more important in older patients with rectal cancer as the population is ageing. The treatment decision made by the modern multidisciplinary colorectal team will recommend pre-operative chemo-radiotherapy followed by surgery for advance rectal cancer and surgery alone for early rectal cancer, as the "standard of care" is surgery. However, an alternative non-surgical treatment option should be consider for older patients with rectal cancer as the surgical harm can far outweigh the potential benefits. There is published evidence that mortality is higher with increasing age. An alternative treatment option to surgery when patients are not suitable or refusing surgery is to offer them external beam radiotherapy (EBRT) or chemo radiotherapy (EBCRT). A proportion of these patients can achieve a clinical complete response (cCR) which enable adoption of 'watch and wait' strategy to avoid surgery. However, a third of patients who achieved initial cCR can develop local regrowth within the first two years. This require salvage surgery which reduces their chance of organ preservation. Contact X-ray brachytherapy (CXB) or High Dose Rate Endo Brachy Therapy (HDREBT) boost following external beam radiotherapy can improve the initial cCR rate and reduce the risk of local regrowth. Those patients with persistent residual cancer or regrowth after brachytherapy boost following EBCRT or EBRT can have salvage surgery later without compromising their chance of cure. Therefore, patients should be fully aware of their treatment options and have 'a choice' when deciding and consenting their treatment.

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Background

The population is ageing [1] and it is important to recognise that chronological age alone may not reflect the functional reserve and life expectancy of an individual patient. The older age group patients are very heterogeneous and ageing is highly individualised. A comprehensive geriatric assessment (CGA) is important to address the diversities in the geriatric population [2]. There is an urgent need to adopt a common assessment language and classify older cancer patients into at least 4 categories according to their P.S. (performance status), CGA and what outcome we are trying to achieve in order to plan their management properly (Table 1 and 2):-

1. Older patients who are fit (PS 0-1) with early stage cancer. In this group, the patients are functionally independent and without significant comorbidity. They are candidates for surgery which is the "Gold standard of care". These patients may refuse surgery as they are stoma phobic.
2. Older patients with advance rectal cancer who are fit (PS 2) but are at high risk for surgery. In this group, patients are functionally independent with one to two comorbid conditions. Surgery is possible but the patients are at high risk for complications (>10%).
3. Older patients with advance rectal cancer (PS 3) who are not fit. In this group, the patients are frail (dependence in one or more activities of daily living, three or more comorbid conditions, and one or more geriatric syndromes). Surgery is not possible and require care and caution for any treatment offer.
4. Older and frail patients with recurrence or metastatic cancer who are not fit (PS 3-4). They are patients mainly for palliative treatment to control their symptoms.

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Older patients with rectal cancer who are fit but refusing surgery

The incidence of cancer increases with age and the majority of patient with rectal cancer are above the age or 65 years [2]. Despite their age, many older patients are fit and can undergo radical surgery which is the standard of care for rectal cancer [3]. However, morbidity and mortality is high with increasing age [4]. External beam chemo-radiotherapy (EBCRT) or radiotherapy (EBRT) is usually offer when patient are fit but refuse surgery [2]. The tolerance of normal tissue and organs at risk (OAR) for older patients are quite similar but due to ageing the limit of tolerance-dose is considered to be lower in most tissues and OAR. However, there is no difference in technique that is use and outcomes are similar when treating patient below or over the age of 65 years. If combine radiation and chemotherapy is plan for older patient, one needs to take into consideration the bone marrow and immune system tolerance. In general tolerance of radiation depends on the treatment volume treated and in older patients smaller volumes should be consider. When treating early stage rectal tumours (cT1), the risk of lymph node spread is relatively low (<10%). We should seriously consider treating only mesorectal field and avoid treating all the lymph node areas we normally use for more advance stage cancer (cT3 and above) where the risk of lymph node spread is much higher (20–40%). In general, concurrent chemo RT has a lot more G3 or G4 toxicity than radiation alone [5]. Therefore, chemo-radiotherapy must be used with extreme caution with careful surveillance. Good tolerance is extremely important in older frail patients because when toxicity occurs it can be life-threatening and very difficult to manage. Therefore, we need to consider alternative radiotherapy options to try and reduce toxicity. One radiotherapy option is to consider brachytherapy either Contact X-ray Brachytherapy (CXB) or High Dose rate Endorectal Brachytherapy (HDREBT) [6–8]. It provides the best benefit/risk ratio as it is the only technique able to deliver accurately a high dose of targeted radiation straight on the tumour using a small volume (<5 cm^3) which minimises the toxicity. It can be deliver as an out patients in a few treatment fractions. Therefore, unlike multiple fractions needed for EBRT, hypo-fractionated brachytherapy is more suitable for older patients as they like to avoid frequent and long distance travelling to receive their radiotherapy.

Older patients with early rectal tumours fit but refusing surgery (CXB alone)

In older patients with small (<3 cm) early (cT1/cN0) rectal cancer, Contact X-ray Brachytherapy (CXB) alone can be offered. The risk of microscopic lymph node spread is usually low (less than 5–10%) and external beam radiotherapy can be omitted to reduce toxicity.

What is contact X-ray brachytherapy (CXB)?

Contact X-ray Brachytherapy (CXB) uses very high dose of low energy X-rays (50 kVp) which is targeted directly on the tumour under visual guidance. As the energy is low the penetration into deeper surrounding normal tissue is limited which reduces the toxicity from radiation. This is a significant major advantage for older patients when considering radiotherapy alone as an option.

Indications for CXB alone.

1. Radical CXB as a sole treatment (monotherapy).
2. Post-operative CXB

Radical treatment for early rectal cancer cT1cN0cM0 (CXB alone without surgery)

Radical CXB alone is suitable for:-

1. Histologically confirmed rectal cancer staged cT1/cN0 less than 3 cm in greatest diameter.
2. Well to moderately differentiated adenocarcinoma.
3. Tumour configuration of non-ulcerative, polypoid mobile tumour.
4. Tumour situated less than 10 cm from the anal verge.

Local excision followed by CXB for early rectal cancer cT1 (post-operative CXB)

When unexpected malignancy is diagnosed in a polyp which was thought to be benign, the standard of care is to offer completion surgery. If the patient is older or fit but refusing surgery as it involves a stoma, CXB can be given as an alternative. External beam radiotherapy can be added if there are adverse factors such as poorly differentiated tumour or presence of lympho-vascular invasion which increases the risk of lymph node spread. Addition of post-operative CXB boost improved local control in 180 patients treated at Clatterbridge who are either not fit or refused surgery [9].

Indications for post-operative CXB.

1. Uncertain resection margin Rx (polyps removed piece meal).
2. Involved resection margin (R1) (after EMR or TEMS)
3. Poorly differentiated adenocarcinoma (consider adding EBRT).
4. Presence of lympho-vascular invasion (consider adding EBRT).

What is the dose of radiation?. The dose of CXB depends on whether the tumour has been removed initially (post-operative) or not. In cases where the tumour has been remove by endoscopic submucosal resection (EMR) or Trans-anal Endoscopic Micro Surgery (TEMS), the dose of CXB is 60Gy in 2 fractions two weeks apart (30Gy per fraction x2).

When CXB is used alone without surgery, then 90 Gy in 3 fractions over 4 weeks is given (30Gy per fraction x 3). Less commonly, 110Gy in 4 fractions over 6 weeks is used for older patients not suitable for surgery with small residual tumour after the 3rd CXB fraction.

How do we do CXB?. Contact X-ray brachytherapy is given as a day patient. Patient is assess initially and previous information regarding CXB is confirm to make sure the patient truly understand their risk and benefits involved. If the patient is fully informed and suitable for CXB, patient signs a consent form before their treatment. The treatment can be given on the same day or another day according to the patient's preference. Patient can be treated either in supine or prone position (Fig. 1). Bowel preparation is carried out with low residue diet for 3 days prior to treatment. Patient is given micro enema 30 min prior to treatment which helps to clear the bowel. Rigid endoscopy is carried out first to locate the tumour size and position. Then suitable treatment applicator size either 30, 25 or 22 mm is selected to cover the tumour with a 5 mm margin. The treatment applicator is position directly over the tumour and low energy (50 kVp) radiation is apply straight on the tumour. The treatment is repeated every 2 weeks to a total of 3 sessions (rarely 4 depending on the response). The tumour is shaved off layer by layer with each treatment session and the tumour regress centripetally

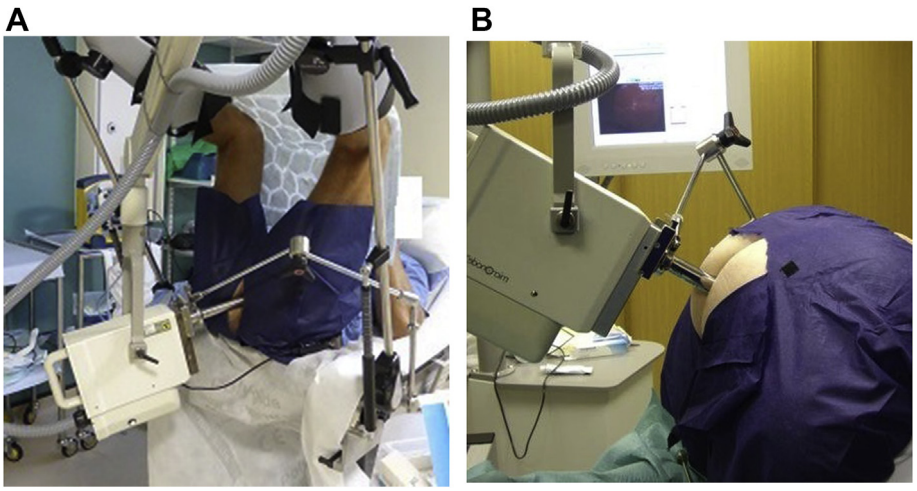

Fig. 1. Treatment position for CXB.

to the origin where it starts. The radiation dose applied is very high (30 Gy) but the radiobiological equivalent dose (EQD^2) is much higher at approximately 100 Gy which is 3 times the applied physical dose at each fractionation. However, although the applied radiation dose seems very high, it is applied directly on to the tumour in a small volume of less than 5 cc^2. Therefore, there is very little collateral damage to the normal surrounding tissues. In addition, the normal tissues recover during the two weeks rest interval during each treatment sessions. In responsive tumour, there is no visible tumour on endoscopy, no palpable tumour on digital rectal examination (DRE), or on radiology. This is known as clinical complete response (cCR) (Fig. 2). No further treatment is necessary and the patients can be registered into a 'watch & wait' protocol [6,7,and8]]. Patients are follow up regularly every 3–4 months with endoscopy, DRE (digital rectal examination) and radiology (MRI and CT scan), especially in the first two years where the risk of local regrowth is highest. Then 6 months to annually up to five years. Any local regrowth detected during this follow-up is confirmed and case discuss at MDT for consideration of salvage surgery.

Older patients with advance rectal tumour who are relatively fit but at high risk for surgery (cT2-cT3/cN1-2)

The standard of care for MRI staged advanced rectal cancer which is inoperable due to threaten or involve Circumferential Resection Margin (CRM) is preoperative chemo-radiotherapy (EBCRT) or external beam radiotherapy (EBRT) [10]. This is followed by extirpative surgery if the tumour regress and becomes operable after restaging scans. However, if there is no residual tumour which can be seen, felt on digital rectal examination (DRE) and if the restaging MRI show significant tumour regression (TRG 0 or TRG 1) with no radiologically obvious residual tumour, then 'watch and wait' approach can be adopted if the patient is keen to avoid surgery or a stoma [11]. However, the probability of achieving a clinical complete response is between 10 and 20%. It is less likely for more advanced staged cT3 or cT4 and bulky (>5 cm) rectal tumour. Published evidence showed pathological complete response was only 10.3% [12]. Moreover, there is 25–30% risk of local regrowth within two years from treatment (Table 2). Salvage surgery is necessary in both these circumstances and the chance of organ preservation will be reduced to less than 40% [11]. Dose escalation has been tried to improve organ preservation but local regrowth was found to be still high and salvage surgery was needed [11]. One novel way to reduce local regrowth is to offer brachytherapy either Contact X-ray Brachytherapy [CXB] (Papillon) [13] or HDR Endorectal Brachytherapy (HDREBT) [14] (see Table 3).

Benefits of additional boost of brachytherapy following EBCRT: -

1. Improves the chance of initial clinical complete response (cCR).
2. Reduce the risk of local regrowth.

Contact X-ray brachytherapy (CXB) as a boost for advanced rectal cancer

There was published evidence to support the benefits of CXB boost. Firstly, there was a randomised trial Lyon 96-02 which demonstrated the benefits of CXB boost after EBRT. Patients with cT2 cT3 tumours were randomised to receive either EBRT 39Gy in 13 fractions over two and a half weeks against the same dose of EBRT followed by CXB using 85Gy every 2 weeks in 3 fractions. At the median follow up of 35 months, a significant improvement was seen in favour of the CXB boost for clinical complete response (24% v 2%) and for a complete or near-complete sterilization of the operative specimen (57% v 34%). This trial showed that the dose escalation with endocavitary irradiation achieved increase tumour response and sphincter preservation with no detrimental effect on treatment toxicity and early clinical outcomes [15]. The main drawback of this trial was external beam radiotherapy dose of 39Gy in 13 fractions which is not the current standard of care accepted for advanced cancer at the present time. In addition, the main end point of sphincter preservation is also not a relevant endpoint at this modern era. There is an ongoing European phase 3 trial OPERA (Organ Preservation in Early Rectal Adenocarcinoma) to evaluate the role of CXB in the modern era. This ongoing trial randomised chemo-radiotherapy using 45Gy in 25 fractions over 5 weeks with concurrent oral capecitabine followed by either EBRT boost (9 Gy in 5 fractions over 5 days) which is the acceptable current standard of care and this is randomised against CXB boost of 90Gy in 3 fractions over 4 weeks. Organ preservation at 3 years is the primary end point and the secondary end points are clinical complete response rate (cCR), toxicity, local disease free survival (DFS), overall survival, difference in quality of life and stoma rates [16] (Fig. 3). This trial is recruiting well and over 100 patients has been randomised, so far. Data is now being reviewed by IDMC on the first 80 patients to evaluate whether there are any unsalvageable local regrowths of more than 10% reported in either arms. We aim to publish this trial

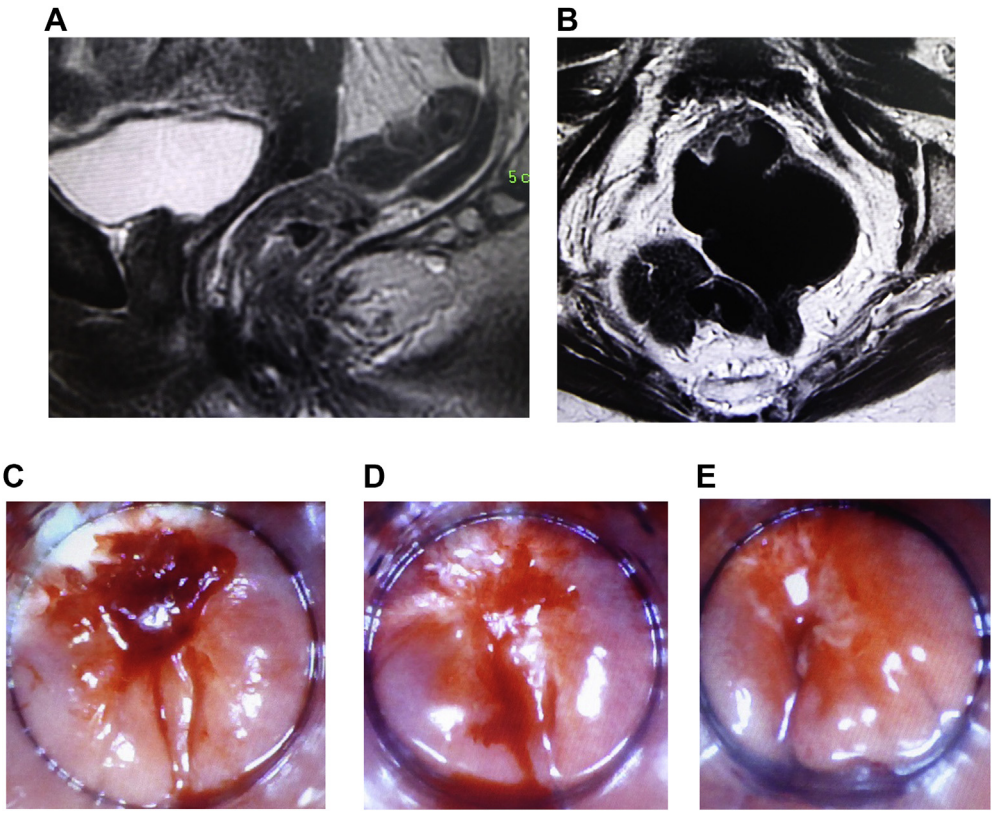

Fig. 2. Treatment response in older patient
Treatment response for CXB
84 year old lady with 2.5 cm low rectal
Endoscopy and Biopsy showed moderately differentiated adenocarcinoma
a MRI pre-treatment (Sagittal)
b MRI staged cT3 cN0 cM0 (Transverse)
She had long course radiotherapy 45Gy in 25 fractions over 5 weeks in Oct–Nov 2018.
There was a minimal residual tumour in the low rectum. Patient is fit for her age but high risk for surgery due to her medical comorbidities. Patient refused surgery and was offered CXB.
c Pre CXB treatment Day 0–28.02.19 (Post EBRT 12 weeks) minimal residual tumour
d Post CXB treatment Day 14–12.03.19 -Residual tumour has regressed
e Appearance 6 weeks after first CXB treatment 09.04.19
Superficial ulceration but no palpable residual tumour.

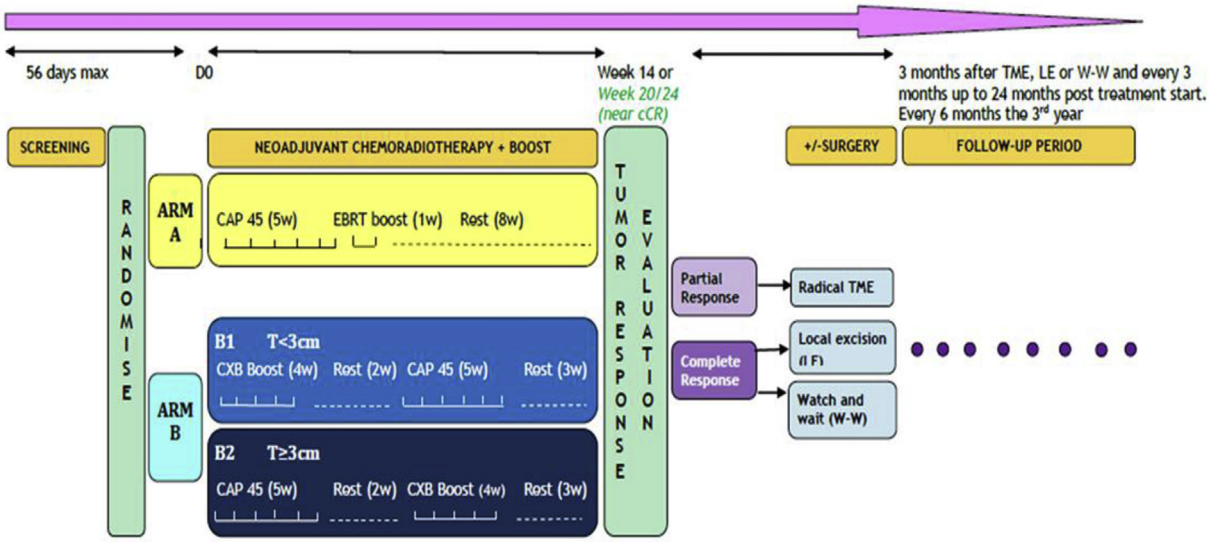

Fig. 3. OPERA trial study design.

Table 1
Patient categories for treatment selection.

1. Older patients with early stage cancer who are fit (PS 0–1).
In this group, the patients are functionally independent and without significant comorbidity. They are candidates for surgery, which is the "gold standard of care". These patients may refuse surgery as they often want to avoid having a stoma.
2. Older patients with advanced rectal cancer who are fit (PS 2) but at high risk of surgical complications.
In this group, patients are functionally independent, with one or two comorbid conditions. Surgery is possible but the patients are at high risk of complications (>10%).
3. Older patients with advanced rectal cancer (PS 3) who are unfit.
In this group, the patients are frail (dependence regarding one or more activities of daily living, three or more comorbid conditions, and one or more geriatric syndromes). Surgery is not possible and any treatment provided requires care and caution.
4. Older frail patients with recurrent or metastatic cancer who are unfit (PS 3–4).
In this group, the patients mainly required palliative treatment to control their symptoms.

Table 2
Treatment options for older patients with rectal cancer.

Patient group	Non-surgical treatment	The standard of care
1. Older fit patients (PS (0-1) with early stage rectal cancer	CXB (alone) cT1/cT2/cN0 TEMS + CXB (Post op)	TEMS (pT1 only)
2. Older fit patients (PS2) with advance rectal cancer	EBCRT + CXB (boost) EBCRT + HDREBT (boost)	EBCRT + TME
3. Older, frail, unfit patients (PS3) with advance rectal cancer	SCRT + CXB or SCRT + HDREBRT	EBRT + EBRT (boost)
4. Older unfit patients (PS 3-4) with recurrence ± metastasis	SCRT/EBRT (palliative) CXB/HDREBT (palliative)	No surgery

Table 3
Comparison of initial response rate and local regrowth rate after cCR.

Study	n	Treatment	Initial response (n/N (%)	Local regrowth n/N (%) with time point
Habr Gama [11]	183	EBCRT (45 Gy) +EBRT boost (9 Gy)	90/183 (49)	28/90 (31 at 5 years)
Appelt [14]	51	EBCRT (60 Gy) + HDR (5 Gy)	40/51 (78)	9/40 (25.9 at 2 years)
Renehan [26]	129	EBCRT (45 Gy)	NA	44/129 (38 at 3 years)
Gerard [6]	45	EBCRT (50 Gy) + CXB (90 Gy)	43/45 (98)	3/43 (11 at 5 years)
Dhadda [8]	42	EBCRT (45 Gy) + CXB (90 Gy)	NA	5/42 (12 at 2 years)
Sun Myint [7]	83	EBCRT (45 Gy) + CXB (90 Gy)	53/83 (63.8)	6/53 (11.3 at 2.5 years)

HDR = high-dose-rate brachytherapy; NA = not available.

at the end of 2022 with 3 years minimum follow up after completion of recruitment in 2019. In the meantime, we can only rely on published data from non-randomised retrospective single institutional studies. Surprisingly, the published data from three different institutions consistently showed reduction of local regrowth [6–8].

The Clatterbridge Cancer Centre has treated over 1600 patients so far and has published their third paper with 200 patients treated between 2003 and 2012. This has shown that initial cCR can be achieved in 68% of patients with minimal residual cancer (<3 cm) following EBRT. More importantly, local regrowths which occurred within the first 2 years can be reduced down to 11%. Those with residual disease after EBRT and CXB can be offered salvaged surgery. In addition, those with local relapse after achieving cCR after CXB boost (11%) can also be salvaged in those who are fit and agreeable for surgery [7]. This data was supported by independent publications from two other centre on different cohort of patients. Hull was the second radiotherapy centre in the UK which offers CXB facility from 2011. Dhadda published his experience on 42 patients treated with CXB and EBCRT without any primary surgical excision. At median follow up of 24 months, local recurrence-free survival was 88%, disease-free survival was 86% and overall survival was 88% which was impressive as many of their patients were older with median age of 78 year (range 50–94 years). This meant most of their older patients were not dying off due to their rectal cancer. The 30 day surgical procedure related mortality for this cohort of older patient was predicted at 12% which was much higher than predicted for younger age group. No patients died directly due to contact radiotherapy procedure. The Hull investigators also assess the functional outcomes as investigated by the Low Anterior Resection Syndrome (LARS) score and they were found to be good, with 65% of patients treated by CXB having no LARS. There were no local recurrences in patients staged as T1N0. With a median follow-up of 24 months, five patients developed a local recurrence (12%), all of whom had been staged as T2N0 initially. This rate of local regrowth concurred with the data from Clatterbridge. The median time to develop local recurrence was 12 months (range 4–14 months) which again was very similar. It concluded that Contact radiotherapy (CXB) for rectal cancer is a safe, well-tolerated outpatient procedure, allowing organ preservation, with excellent oncological and functional outcomes. For older co-morbid patients with suitable rectal cancers this should be considered as a standard of care [8]. The third paper on CXB boost after EBCRT was published from Gerard's group in Nice. The French experience was similar to both Clatterbridge and Hull in that only 11% of their patients developed local regrowth after the median follow-up time was 60 months [95% CI:52-109]. Clinical complete response (cCR) was achieved in 43 patients (96%) with a small residual ulceration present 1–6 months after treatment in 15 of the patients. This ulceration was painless and healed spontaneously but two patients underwent an elective local excision. Histology of one patient showed no residual cancer (ypT0) and the other showed few residual cancer cells (ypT1) [7]. There were many inhomogeneity in treatment strategies with different radiation dose both for CXB and EBRT. And also the sequence of treatment delivery either CXB first or EBCRT with some having additional Iridium boost in addition to CXB and EBRT. It reflected the real world scenario and this inhomogeneity was also seen in the Clatterbridge data. However, the

outcome in reducing local regrowth and high clinical complete responses appeared similar in all these three institutions [6–8]. The common denominator CXB appeared to play a significant role.

High dose rate endo rectal brachytherapy (HDREBT) boost for advance rectal cancer

This procedure can be used as a sole procedure or in addition to EBCRT. It uses radioactive source either Iridium (Ir^{132}) or Cobalt (Co^{60}) unlike CXB which uses low energy 50 kVp X-rays. High dose Rate Endorectal Brachytherapy (HDREBT) was first used by Japanese investigators as a preoperative radiotherapy option following EBCRT for advanced rectal cancer, to improve surgical outcomes. Investigators from Montreal continued with this research at McGill University and later at Jewish Hospital to evaluate the efficacy of neoadjuvant brachytherapy for locally advance rectal cancer (LARC). High dose rate endoluminal brachytherapy was used only to deliver 26 Gy over 4 consecutive days. They reported on 49 patients with T2 to early T4 operable tumours treated by HDREBT without any EBCRT. All patients had surgical resection after 4–8 weeks after their brachytherapy. Histology of resected specimen showed 32% of patients had pCR and further 36% had only microscopic residual disease at the primary tumour site [17]. The extension of this study reviewed 100 patients with low cT2 and T3 tumour using the same brachytherapy regimen. At median follow-up time of 63 months, they reported 27% of patients achieved ypT0N0 [18]. Investigators from Liverpool reported on 34 patients (median age 67 (range 39–81) years. Twenty-nine patients had surgery following CRT and brachytherapy boost. Twenty-four (83%) patients had an RO resection compared with 63% having conventional preoperative CRT using bolus 5FU regimes. Pathological complete remission (pCR) was achieved in 9 (31%) compared with 12% patients having conventional CRT. There was no increase in G 3–4 toxicity from RT and no delay in wound healing or increase in anastomotic leakage [19]. The Danish group investigated the feasibility of chemoradiation combined with endorectal brachytherapy in advanced T3 rectal cancers with complete pathological remission (pCR) as the primary endpoint [20]. Brachytherapy was given using the Nucletron micros electron HDR after loading system. The treatment was given as a single fraction of 5 Gy at 10 mm from the applicator surface and the treated area was the residual tumour bed. Forty-eight patients had surgery 4–6 weeks later. Thirteen patients (27%) had no residual tumour (ypT0). Following their encouraging results, the Danish investigators set up a randomised trial to evaluate the role of HDR brachytherapy boost following EBCRT. They included 248 patients with T3-4N0-2M0 rectal cancer were prospectively randomized to either long-course preoperative CRT (50.4 Gy in 28 fractions, per oral tegafur-uracil and L-leucovorin) alone or the same CRT schedule plus a brachytherapy boost (10 Gy in 2 fractions). Despite a significant increase in tumour response at the time of surgery, no differences in 5-year OS (70.6% vs 63.6%, hazard ratio [HR] = 1.24, P = .34) and PFS (63.9% vs 52.0%, HR = 1.22, P = .32) were observed. They concluded that despite increased pathologic tumour regression at the time of surgery it did not necessarily lead to a relevant clinical benefit when the neoadjuvant treatment is followed by high-quality surgery [21]. NICE (IPG 531) has reviewed the role of preoperative HDR endoluminal brachytherapy in rectal cancer and concluded that current evidence on the safety of preoperative high dose rate brachytherapy for rectal cancer and its efficacy in reducing tumour size appears adequate. However, there is no evidence that the procedure provides additional benefit when used as a boost to external beam radiotherapy. Evidence on the efficacy of the procedure if used without external beam radiotherapy is inadequate in quantity. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research [22].

A brachytherapy dose finding study was performed by the Dutch investigators in 38 inoperable/older patients with T2-T4 and N0-1 rectal cancer. Patients received EBRT (13 × 3 Gy) followed by three weekly HDREBT applications (5–8 Gy). Acute grade 2 and 3 proctitis occurred in 68.4% and 13.2% respectively while late grade 2 and ≥ 3 proctitis occurred in 48% and 40%. In three patients frank haemorrhage or ulceration occurred. Most severe toxicity was observed 12–18 months after treatment. They concluded that for older patients with rectal cancer, definitive radiotherapy can provide good tumour response but has a substantial risk of toxicity. The potential benefit and risks of a HDREBT boost above EBRT alone needs to be further evaluated [23].

Contact X-ray brachytherapy or HDR rectal endoluminal brachytherapy (HDREBT)?

Both CXB and HDREBT are attractive for older patients with early rectal cancer as they are highly targeted treatments with much less side effects compared to external beam radiotherapy especially when use concurrently with chemotherapy. Both can be used solely to treat early rectal cancer as the risk of lymph node metastases is small (<10%). In addition, both these treatment modalities use hypo fractionated regimes as outpatient which mean less visit to hospitals and no hospital inpatient stay for the patients. The treatment regime use for CXB has been developed over the past 80 years and the protocol adopted by most centres has been fairly standardised. HDREBT treatment on the other hand is more variable with four consecutive days in Montreal and weekly in other centres. The volume which HDREBT treat is much bigger than CXB which could account for more side effects mainly bleeding and proctitis. However, HDREBT is more suitable for treating bigger volume rectal tumours and those situate high in the rectum which cannot be reached by CXB treatment applicator (>10 cm from anal verge).

Older patients with advance cancer who are not fit for surgery

Older patients with advanced rectal cancer not fit for surgery are usually offer either SCRT or EBCRT depending on their fitness for chemotherapy [2]. If EBCRT is proposed for an older patient, dose reduction should be consider to reduce toxicity. It is also true that patient above 80 years like to avoid frequent and long distance travelling to receive radiotherapy. For these reasons there is a general trend in these older patients especially if they are frail to propose a short course radiotherapy (SCRT) schedule using smaller irradiated volume and aim for ambulatory treatment with few immediate side effect or toxicity. A small number of patients with advance tumour can achieve a complete clinical response (cCR) as with patients who are fit for surgery. However, there is no option for salvage surgery in the event of local regrowth. Unlike the early tumour, the majority of patients with advanced rectal cancer do not respond as well to EBRT and the chance of pCR is less than 10% [12]. The majority of patients have a residual cancer which will develop a regrowth within 12–18 months. Salvage surgery is not possible and patient needs a referral to palliative care services for symptom control. Therefore, additional CXB boost in patients with minimal residual disease should be consider to improve local symptom control [6–8]. The chance of cure is low and the treatment is offer mainly to control symptoms. There are no randomised trials published or set up currently to evaluate this.

The role of radiotherapy for palliation in recurrent rectal cancer

Small recurrences

Contact X-ray brachytherapy can be used to control symptoms from a small recurrent rectal cancer at the anastomotic site in patients who are not fit or refusing further salvage surgery. CXB is a highly targeted treatment with limited risk of toxicity. It is highly unlikely that CXB can eradicate the recurrent cancer as they do not usually respond to radiotherapy [7]. However, a good symptom can be achieved. If the recurrent tumour is not suitable for CXB, then HDREBT can be used instead. Investigators from Mount Vernon reported a series of 50 patients who received hypo fractionated HDREBT using single line source in one to six fractions. The most common presenting symptom was bleeding per rectum for which a 64% response rate was obtained with 57% complete responses. Mucous discharge responded in 64% with 28% complete responses. The median duration of response was 7 months. They concluded that intraluminal HDR brachytherapy was an effective local treatment for patients otherwise unfit for radical surgery both as a component of radical treatment, or as a simple single palliative procedure [24].

Advance extensive recurrences

Patients may present with painful advance bulky recurrences following previous surgical resection will need palliation of their symptoms. Clinicians are reluctant to re-irradiate in these patients if they has been previously treated with radiation typically receive what has historically been considered a lifetime dose of pelvic radiation. However, there is some evidence to suggest that re-irradiation therapy using either external beam radiotherapy or chemo-radiotherapy may be an appropriate option to consider in this group of patients. One retrospective study reported the results of 52 patients receiving re-irradiation for palliation in this scenario. Patients received between 19.8 and 40.8 Gy, and all patients reported initial control of bleeding, and palliation of pain was achieved in 65% [25].

Discussion

The decision made at the modern multidisciplinary colorectal cancer team meeting (MDT) will recommend pre-operative chemo-radiotherapy followed by surgery for advance rectal cancer and surgery alone for early rectal cancer, as 'the standard of care' for patients with rectal cancer is surgery which is approved by national and international guidelines and protocols [3,10]. However, if the patients are not suitable for surgery or refusing surgery, an alternative is to offer EBCRT or EBRT [11]. There is a chance of clinical complete response (cCR) which avoid extirpative surgery and a stoma. However, approximately a third of patients will develop a local regrowth which require salvage surgery in patients who are fit and agreeable [26]. This reduces their chance of non-surgical treatment with organ preservation and avoidance of a stoma. One option is to escalate the dose of radiation to the primary tumour which can reduce the tumour local regrowth in this area. Radiation dose escalation can be done by brachytherapy boost following EBCRT or EBRT either using Contact X-ray Brachytherapy (CXB) [6–8] or High Dose Rate Endorectal Brachytherapy (HDREBT) [17–19]. The choice of which type of brachytherapy boost depends on the bulk of residual tumour. If the residual tumour is less than 3 cm then CXB can be used. However, if the size of residual tumour is more than 3 cm, then HDR brachytherapy is more suitable as it can treat larger areas using a dedicated rectal brachytherapy applicators.

Contact X-ray Brachytherapy (CXB) has been used to treat rectal cancer for over the past 90 years. The initial use of rectal brachytherapy using low energy X-rays was started before the Second World War by Siemens Company (Berlin, Germany). After the war, Phillips Company (Eindhoven, Netherlands) started the production of RT 50 until the mid-seventies. This was the machine first used by Lamarque and Gros from Montpellier [27]. The most important contribution made by them was to introduce a new method of local treatment of rectal cancer, but more importantly they defined the cases suitable for such irradiation. The concept of delivering high dose of radiation given in few fractions every 2–3 weeks over a long period was completely opposed to the principles of conventional X-ray therapy where the dogma was to give low dose of radiation in multiple fractions given daily over four to five weeks in order to reduce radiation toxicity.

Prof. Papillon popularised the CXB technique which bears him [13,27]. Papillon observed that configuration and size of the rectal cancer were important. Polypoid tumour respond to treatment better than deeply infiltrative ulcerative tumours and the local failure was low at 3.8% compared with 10.2% for ulcerative tumour. The size of more than 3 cm has local failure rate of 10.5% compared to 4.6% for smaller tumour. He stressed that case selection was important to achieve the best outcomes. Many of his patients were older and only 58% were alive at 10 years. However, only 10% were cancer related deaths and many of his patients (29.4%) died from intercurrent disease [27]. Papillon protégée Jean Pierre Gerard continued treating rectal cancer with CXB [28]. Gerard initiated a randomised trial Lyon 96-02 using external beam radiotherapy with or without CXB to demonstrate that there was a role for CXB in the management of rectal cancer. There was higher complete clinical response, lower local regrowth and much higher sphincter preservation the CXB arm [15]. The weakness of this trial was the radiation used was out dated regime with no concomitant chemotherapy which is now the standard of care. International Contact X-ray radiotherapy Network group (ICONE) has now set up a European phase 3 randomised trial which will evaluate the role of CXB following EBCRT (the standard of care) against EBCRT with EBRT boost [16]. This trial is recruiting well and we aim to publish our preliminary results in 2022 after 3 years follow up.

There were at least two large randomised trial published which showed chemo-radiotherapy was better than radiotherapy alone in improving disease free survival for advanced rectal cancer cT3 cT4 [5,29]. However, the combined modality treatment has a lot more side effects and caution is necessary for its use in older patients who can be frail and with multiple comorbidities. Therefore, chemotherapy should be use with caution or even omitted in older patients with poor renal function. However, short course radiotherapy (SCRT) can be used alone for operable early stage rectal cancer. Russians were the first to use SCRT followed by immediate surgery in operable rectal cancer. Swedes started a randomised trial comparing surgery alone against SCRT followed by surgery. Both local control and survival were improved compared to surgery alone [30]. The high local recurrence rates from surgery alone in Swedish trial was considered to be due to poor surgical techniques used. The Dutch then repeated this trial with much better trained colorectal surgeons. Prof Bill Heald from Basingstoke helped the Dutch team with the surgical training. Despite better surgery which improved the local control, the Dutch TME (Total mesorectal Excision) trial showed that addition of SCRT improved local control further when compared to surgery alone [31]. Medical Research Council (MRC) from the UK then carried out the third and final short course pre-operative radiotherapy trial (CR07) for operable rectal cancer. Surgery alone carried out by properly trained colorectal surgeons was randomised against preoperative SCRT

followed by surgery [32]. Despite better surgical technique the trial showed much better local control even for those patient with best surgical plane (mesorectal) when pre-operative SCRT was used compared to surgery alone [33]. Unfortunately, despite level 1 evidenced from 3 large randomised trials, involving over 4000 patients treated over 3 decades, SCRT with immediate surgery is no longer used by most colorectal centres around the world. However, SCRT is suitable for older patients with early rectal tumours who are frail and especially in those with poor renal function where the use of chemotherapy can be challenging. SCRT is much better tolerated in older patients and added bonus is less visits to hospital which suits the patients if they are main carers for their partners. There was published data on the benefits of SCRT for more advanced rectal cancer where a longer interval wait is necessary to achieve down staging before assessment [34,35]. It is difficult to recruit older and frail patients who are not fit for surgery into randomised control trials. However, NCRI (National Research Institute, UK) have now developed the APHRODITE study which is a phase II dose escalation study using external beam alone. This trial will evaluate different dose of radiation to achieving organ preservation in a frail population where radical surgery is considered high risk and therefore not the standard of care [36]. In addition, researcher from John Hopkins University have also set up a rectal brachytherapy trial comparing Chemoradiation OR brachytherapy for Rectal Cancer (CORRECT). This trial compares chemoradiotherapy (the standard of care) with HDREBT in patients suitable for chemotherapy and surgery. Adjuvant chemotherapy with FOLFOX 12 cycles in both arms [37]. The results from these trials will contribute to our present understanding of the role of radiotherapy in older patients.

Conclusion

Radiotherapy has a role in the management of both early and locally advanced rectal cancers in older patients. The concept of using radiotherapy for early rectal cancer in older patients can be challenging, as the standard of care is surgery. However, it offers an advantage of non-surgical treatment option to allow 'watch and wait' strategy in those who respond well to radiation. Brachytherapy either with CXB or HDREBT can be used as a boost in patients with minimal residual disease after EBRT or EBCRT. This approach can avoid surgical harm and a stoma which older patients prefer not to have, if they have a choice. In future, we hope more non-surgical trials using novel radiation techniques in rectal cancer will be set up to shed some light on many unanswered questions, which may help to provide some evidence base data on how best to manage older patients with both early and advanced rectal cancer.

Declaration of competing interest

ASM- No conflict of interest to declare.
JPG - Medical advisor to Ariane Medical Systems.

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