

Non-operative treatment after neoadjuvant chemoradiotherapy for rectal cancer

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The past decade has seen pronounced changes in the treatment of locally advanced rectal cancer. Historically, the standard of care involved surgery followed by adjuvant radiotherapy or chemoradiotherapy. More recently, the emergence of neo-adjuvant chemoradiotherapy has fundamentally changed the management of patients with locally advanced disease. In clinical trials, pathological complete responses of up to 25% have raised the question as to whether surgery can be avoided in a select cohort of patients. A trial of omission of surgery for selected patients with complete response after preoperative chemoradiotherapy has shown favourable long-term results. In this article, we outline emerging factors for achieving pathological complete response, non-operative strategies to date, methods for prediction of response to chemoradiotherapy, and future directions with the addition of MRI as a radiological guide to complete response.

Introduction

More than 13 000 people are diagnosed with rectal cancer in the UK each year. In three-quarters of cases, the disease will be localised to the primary site. For these patients, surgical resection will constitute the cornerstone of treatment. Many patients with T3, T4, and node-positive rectal cancers will be referred for preoperative chemoradiotherapy (CRT) to reduce the risk of local failure and to ensure negative margins at surgery.

In a landmark study, Habr-Gama and colleagues¹ presented long-term results of avoidance of surgery for selected patients with radiological and clinical evidence of complete response after neoadjuvant CRT. Long-term follow-up confirmed the safety of this approach. Modern rectal surgery is not without morbidity, and many patients wish to avoid the permanent stoma associated with abdominoperineal excision. However, preoperative treatments have developed to such a degree that pathological complete responses (pCR) can reach 25% at the time of surgery. With the premise that a pCR might represent needless surgery, an understanding both of the factors that contribute to achieving pCR, and of methods that predict response to CRT, might aid the safe selection of appropriate patients for omission of surgery after CRT (figure 1).

Preoperative versus postoperative CRT

Postoperative radiotherapy or CRT has been the standard of care for many years for stage II and III rectal cancer.²⁻⁵ As a result, pCR cannot be considered a relevant endpoint in assessing the effect of this approach. Postoperative radiotherapy has several theoretical disadvantages. For example, residual neoplastic cells within a hypoxic postoperative tumour bed are poorly oxygenated and, therefore, their sensitivity to radiation is decreased. Furthermore, when surgery precedes radiotherapy there is a risk of tumour spillage into the preoperative bed; this can be reduced by preoperative sterilisation. Finally, the small bowel can settle deeper into the pelvis after surgery and becomes fixed by adhesions, thereby increasing the volume of the bowel exposed to radiation, and increasing the toxic effects.

Two prospective randomised trials in the USA (the National Surgical Adjuvant Breast and Bowel Project [NSABP] R-03 trial⁶ and the Intergroup 1047 trial), compared preoperative and postoperative CRT for patients with locally advanced rectal tumours. Unfortunately, both trials were closed prematurely as a result of poor accrual. The seminal German CAO/ARO/AIO-94 trial⁷ successfully randomised 823 patients with T3, T4, or node-positive rectal cancers to preoperative or postoperative treatment. Preoperative treatment consisted of 50.4 Gray (Gy) in 28 fractions of 1.8 Gy per day for 5½ weeks with continuous infusion of fluorouracil (1000 mg/m² per day, for 5 days) during the first and fifth week of radiotherapy. The postoperative group received the same CRT, although a 5.4 Gy boost was delivered to the tumour bed. Four 5-day cycles of bolus fluorouracil (500 mg/m² per day) four weeks apart were administered adjuvantly either 1 month after surgery in the preoperative group, or 1 month after CRT in the postoperative group.

5-year cumulative local relapse was 6% in the preoperative group versus 13% in the postoperative group ($p=0.006$). Grade III and IV acute toxic effects (27% vs 40% in the

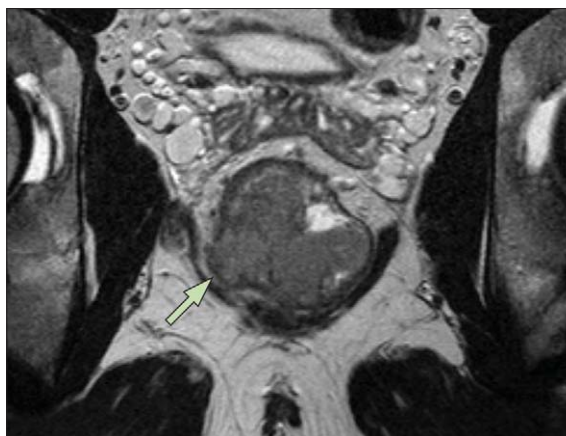


Figure 1: Axial T2-weighted MRI of T3 low rectal tumour with infiltrative border (arrow)

Complete response was achieved after CRT, and the patient was managed non-operatively. 18 months after diagnosis there was no evidence of recurrence.

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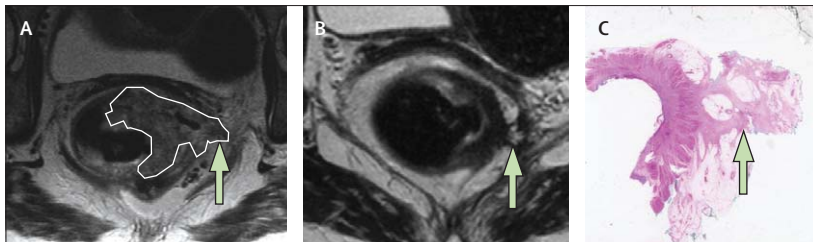


Figure 2: Preoperative and postoperative MRI, with corresponding histopathology, of a pCR after preoperative CRT

(A) Axial T2-weighted MRI of T3 rectal tumour (outlined) extending to mesorectal fascia (arrow). (B) Low-signal intensity replaces tumour extension 4 weeks after CRT (arrow). (C) Histopathology confirms fibrosis (arrow).

preoperative and postoperative groups, respectively; $p=0.001$) and chronic toxic effects (14% vs 24%; $p=0.01$) were more frequent in the postoperative group. Overall survival was equivalent (76% vs 74%; $p=0.80$).

These results of the CAO/ARO/AIO-94 trial have contributed to a paradigm shift, such that preoperative treatment has been widely adopted as the standard of care for locally advanced rectal cancer, and postoperative radiotherapy in this setting has become almost redundant. Preoperative trials have the capacity to report surgical and histopathological outcomes, including pCR (figure 2), and, thus, pCR has become a surrogate endpoint for comparing the effectiveness of preoperative strategies.

Factors affecting pathological complete response

The process of tumour response to CRT, or downstaging (the process of reduction in T or N stage after preoperative treatment), is dependent on many factors. Each of these factors must be considered individually when reviewing response rates in treatment protocols, and when designing preoperative or non-operative strategies.

Tumour stage and size

Tumour regression grading (TRG) is a pathological grading system based on the histological degree of tumour regression and fibrosis present in a rectal cancer specimen after preoperative treatment.⁸ TRG has proven to be of prognostic significance when assessed in 385 patients receiving preoperative CRT within the CAO/ARO/AIO-94 trial, an assessment that also confirmed that tumour stage is crucially important in establishing the probability of downstaging and pCR.⁹ TRG 4 (no viable tumour cells, a pCR) was seen in 25% of T2, 10.1% of T3, and no T4 tumours (based on TNM staging system). TRG was significantly correlated with pathological T stage ($p=0.03$), N stage ($p=0.001$), and the International Union Against Cancer (UICC) stage¹⁰ ($p<0.001$). 5-year disease-free survival was 86% for TRG 4, 75% for TRG 2 and TRG 3 grouped together, and 63% for TRG 0 and TRG 1 grouped together ($p=0.06$).

Tumour size should also be influential in predicting tumour response, and, indeed, the size of rectal tumours, measured on preoperative CT, has been correlated with

pCR after CRT in some studies.^{11,12} Therefore, in addition to traditional staging parameters, the recording of tumour size on preoperative imaging and at pathological assessment is useful.

Radiotherapy

Adenocarcinoma of the rectum is a radiosensitive tumour, and radiotherapy has the potential to eradicate the disease as a sole modality. Radical curative doses for adenocarcinoma at other sites would normally be considered to be greater than 70 Gy. However, rectal cancer cannot be treated at this dose with standard external-beam radiotherapy and conventional volumes, because rectal and small-bowel toxicity would be unacceptable. Standard preoperative external-beam radiotherapy delivers a dose of around 45 Gy to the pelvis, with a boost of radiation between 50.4–54 Gy to a reduced volume encompassing the tumour. However, when radiotherapy is to be the only treatment for rectal cancer, the dose must be escalated in order to achieve optimum local control. To overcome the problem of toxic effects in healthy tissue, studies using radiotherapy alone have incorporated endocavitary irradiation,^{13,14} in conjunction with either interstitial brachytherapy¹⁵ or external-beam radiotherapy,¹⁶ or both. Using this approach, administration of doses in excess of 100 Gy have produced acceptable toxic effects, as shown in a French trial¹⁶ where 63 patients with T2–T3, N0–N1 rectal cancer, who were treated with radiotherapy alone, received endocavitary radiotherapy at a dose of 80 Gy in three fractions, then external-beam radiotherapy at a dose of 39 Gy in 13 fractions with a 4 Gy boost, followed by 20 Gy via a ¹⁹²Ir implant. Despite the high rectal dose delivered in this trial, toxic effects were modest, with no grade 3 or 4 acute toxic effects seen. Late rectal bleeding occurred in 38% of patients, although only one patient needed a transfusion. Anorectal function was excellent or good in two-thirds of patients assessed (Memorial Sloan Kettering scale), and no patients needed a colostomy. Cancer outcomes were also encouraging, with 5-year survival of 84% and 53% for T2 and T3 tumours respectively, for patients <80 years of age. Other studies on early-stage, resectable rectal cancer treated with radiotherapy alone have shown 5-year survivals of 50–90%, with many of the deaths that do occur being caused by intercurrent illness.^{13,17–19} This strategy is often reserved for those unfit for general anaesthesia, although refusal of abdominoperineal excision can also be an indication.

Results such as these establish the effectiveness of radiotherapy as a curative modality for rectal cancer. In this setting, high doses can be safely administered to a small peritumoral area. These data also compliment evidence of a dose–response relation for rectal adenocarcinoma (ie, dose escalation will enhance tumour control and result in a therapeutic gain).^{20,21} This relation is of great importance where downstaging of the tumour is needed.

Concomitant chemotherapy

Key advances have been made in recent years regarding the addition of chemotherapy to preoperative radiotherapy regimens. Concomitant chemotherapy with a fluoropyrimidine is the most common approach in order to augment the local response. Impressive rates of downstaging and pCR can result from the addition of induction chemotherapy, usually with new agents, such as oxaliplatin.^{22,23} However, interpretations of response rates in these trials should be made with caution, because fundamental aspects, such as radiation dose and chemotherapy agent, might be different (table 1).

Two randomised trials have shown the efficacy of concomitant chemotherapy. The European Organisation for Research and Treatment of Cancer (EORTC) has published preliminary and 5-year results of its EORTC 22921 trial, randomising over 1000 patients with T3 or resectable T4 tumours into a 2x2 factorial design: preoperative radiotherapy alone; preoperative CRT; preoperative radiotherapy with four cycles of adjuvant chemotherapy; or preoperative CRT with four cycles of adjuvant chemotherapy.²⁴ Chemotherapy was fluorouracil (350 mg/m² per day) and folinic acid (20 mg/m² per day) for all groups, during the first and last week of radiotherapy, or as four courses every 3 weeks adjvantly. Radiotherapy was 45 Gy in 25 fractions over 5 weeks in all groups. Patients in the CRT groups had smaller tumours on pathological assessment ($p<0.0001$), and greater downstaging ($p<0.001$) than those in the radiotherapy groups. A pCR was seen in 5.3% of patients in the radiotherapy groups and 13.7% of patients in the CRT groups. Results from 5-year follow-up show a local-control advantage (incidence of local recurrence as a first event) for the three groups that received some form of chemotherapy (7.6–9.6%), compared with radiotherapy alone (17.1%, $p=0.002$).

These results are confirmed by a similar French trial with a more straightforward randomisation of preoperative radiotherapy versus preoperative CRT, in which both groups ($n=733$) received four cycles of adjuvant chemotherapy.²⁵ Radiotherapy and chemotherapy were delivered using an almost identical regimen as that used in the EORTC 22921 trial. The incidence of pCR was significantly increased by the addition of concomitant chemotherapy (3.7% vs 11.7%, $p<0.0001$). However, grade 3 and 4 toxic effects were increased in the CRT group (2.7% vs 14.6%, $p<0.0001$). 5-year overall survival was not improved by the addition of concomitant chemotherapy in either trial.

Integrating new agents into preoperative strategies

In the trials discussed above, concomitant chemotherapy did not produce a significant reduction in the risk of metastatic recurrence. This finding implies that concomitant chemotherapy, whether by inadequate dose or choice of agent, achieves only a radiosensitising effect within the pelvis, rather than a significant effect on metastatic microscopic disease. Therefore, preoperative strategies using new agents on an induction or concomitant basis have been investigated in an attempt to address this problem.

The initial results of the EXPERT trial (a phase II study of oxaliplatin, capecitabine, and pre-operative radiotherapy for patients with locally advanced and inoperable rectal cancer) have been reported.²² Eligible patients had MRI-defined poor-risk features including tumour extension within 1 mm or beyond of the mesorectal fascia, T3 tumours at or below the levators, tumour extending 5 mm or more into perirectal fat, and T4 or T1–4 N2 tumours. This trial delivered 12 weeks of neoadjuvant chemotherapy to 77 patients, consisting of four cycles of intravenous oxaliplatin (130 mg/m² every 3 weeks) and

Trial	n	Disease stage	Preoperative chemotherapy	Preoperative RT, Gy	Interval to surgery, weeks	pCR
Habr-Gama ¹	265	T2–T4	Concomitant fluorouracil and folinic acid	50.4	8 to assessment	27% (observation group); 7% (surgical group)
EXPERT ²²	77	Low T3; CRM threatened; tumour \geq 5 mm into mesorectum; T4; T1–T4 N2	Induction: oxaliplatin and capecitabine; Concomitant: capecitabine	50.4–54	6	24%
RTOG 0012 ²³	106	Distal T3 or T4	CVI fluorouracil; or CVI fluorouracil and irinotecan	55.2–60; or 50.4–54	7	26% both groups
EORTC 22921 ²⁴	1011	T3 or T4	Fluorouracil and folinic acid	45	5.4	5.3% (radiotherapy-alone group) vs 13.7% (CRT groups)
FFCD 9203 ²⁵	733	T3 or T4	Fluorouracil and folinic acid	45	3–10	3.7% (radiotherapy-alone group) vs 11.7% (CRT group)
CORE ²⁶	85	Low T3; CRM threatened; T4; T1–T4 N2	Oxaliplatin and capecitabine	45	6–8	13%
CALGB 89901 ²⁷	32	T3 or T4	Oxaliplatin and fluorouracil	50.4	4–6	25%*

*25% pCR in 32 patients on phase II oxaliplatin dose. RT=radiotherapy. CRM=circumferential resection margin. RTOG=Radiation Therapy Oncology Group. CVI=continuous venous infusion; EORTC=European Organisation for Research and Treatment of Cancer. FFCD=Fédération Francophone de Cancérologie Digestive. CORE=capecitabine, oxaliplatin, radiotherapy, and excision. CALGB=Cancer and Leukemia Group B.

Table 1: Selected trials of preoperative CRT for rectal cancer

oral capecitabine (2000mg/m² per day, for 14 days every 3 weeks), before CRT, 45 Gy in 25 fractions over 5 weeks with a 5.4–9 Gy boost delivered to the primary tumour (total dose 50.4–54 Gy) with concomitant capecitabine (1650 mg/m² per day). 67 patients proceeded to appropriate surgery after an interval of 6 weeks with total mesorectal excision. A pCR occurred in 24% of patients and a further 48% were noted to have residual microscopic disease only.

In a preclinical setting, oxaliplatin has been shown to have radiosensitising qualities.²⁸ Trials have used oxaliplatin on a concomitant basis, and the CORE (capecitabine, oxaliplatin, radiotherapy, and excision) group have reported their preliminary findings.²⁶ 87 patients with locally advanced rectal tumours (MRI-defined tumour penetrating or ≤2 mm from mesorectal fascia, or any T3 or T4 tumour <5 cm from anal verge) received concomitant oxaliplatin, capecitabine, and radiotherapy (XELOX-RT): 50 mg/m² oxaliplatin per week; 825 mg/m² capecitabine per day; and 45 Gy of radiotherapy over 5 weeks. Six cycles of adjuvant XELOX-RT were administered to patients with clear or microscopically positive margins. A pCR occurred in 13% of patients (95% CI 5.46–20.34) with acceptable toxic effects. TRG showed an excellent response in 35% of patients, with a poor response in 64%.

The Cancer and Leukaemia Group B 89901 study²⁷ also confirmed the safety of concomitant oxaliplatin, with further clinical evidence of radiosensitisation. This phase I/II trial established the maximum tolerated dose of weekly oxaliplatin on a concomitant basis at 60 mg/m², with continuous infusion of fluorouracil (200 mg/m² per day) and radiotherapy (up to 50.4 Gy). Eight of 32 patients (25%) treated at this dose achieved a pCR.

Concomitant chemotherapy is a major contributor in the downstaging of tumours and in the achievement of a complete response, and has been widely accepted. The use of newer agents, like oxaliplatin, in neoadjuvant protocols might enhance this process further. Preoperative trials incorporating new agents, such as cetuximab, are currently accruing.

Interval to surgery

The effect of radiotherapy on tumour, and consequent tumour response, is variable both in extent and duration. Because response to radiotherapy is a continuous process, the optimum interval between completion of radiotherapy and surgery, and indeed when a meaningful response has been completed, is not clear. Only one randomised trial, Lyon 90-01,²⁹ has investigated the question of optimum interval. This study showed a pCR (or a few residual tumour cells) in 10.3% of patients who had a short interval between neoadjuvant radiotherapy and surgery compared with a pCR in 26% of patients who had a long interval ($p=0.005$). 201 patients with palpable T2 or T3 rectal tumours were randomly assigned to either an interval of 2 weeks or an interval of 6–8 weeks. The

radiotherapy regimen was not typical, 39 Gy at 3 Gy per fraction, approximately equivalent to 50 Gy given at 2 Gy per fraction, and concomitant chemotherapy was not used. Long-term follow-up has not shown any significant differences in toxic effects, local control, or survival.³⁰ These findings suggest that response to radiotherapy continues for a period of up to 6–8 weeks. No reliable clinical data exists to define the degree of response after this period, although it is reasonable to assume that some rectal adenocarcinomas might achieve a complete response after a 6–8 week interval. These findings are of relevance to non-operative protocols, in which tumours need to be allowed sufficient time to achieve complete response.

Short-course preoperative radiotherapy (SCPRT; five fractions of 5 Gy over 5 days) has been used to reduce the occurrence of local relapse for rectal cancer.^{31–33} Although SCPRT produces a reduction in tumour bulk, a downstaging effect has not been seen, with surgery 1 week after radiotherapy.³⁴ Whether or not a longer interval would aid a downstaging effect for SCPRT is not known. However, this question might be answered by an ongoing Swedish randomised controlled trial, comparing three groups: SCPRT with a standard short interval; SCPRT with a 6–7 week interval; and long-course CRT (50 Gy over 5 weeks) with a 6–7 week interval. Thus, for the time being, SCPRT should not be considered standard treatment where downstaging is needed.

Diagnosis of pCR

A common concern when interpreting the incidence of pCR in trials is that the extent of pathological assessment might not be uniform. The Royal College of Pathologists (London, UK) has published guidelines for a minimum dataset for histopathology reports of colorectal cancer.³⁵ However, as a minimum dataset, this does not address the issue of pCR, and there are no guidelines specifying the detail of the examination necessary to establish pCR. Therefore, there are concerns that a bias exists in the interpretation of a pCR incidence in trials. The boundary between categorisation as pCR or as minimum microscopic disease has the potential to be operator dependent in the absence of standardisation of reporting.

A welcome initiative towards standardisation of pCR reporting has been proposed by the CORE group.^{26,36} In their method, the entire MRI-defined pretreatment tumour area is embedded, and at least five tumour blocks are sampled. If a pCR is diagnosed on initial examination, then three sections only are examined from each tumour block. Such a standard should be adopted in other trials.

Omission of surgery for complete responders to preoperative treatment

The impressive incidence of pCR in recent trials raises the possibility of selecting patients who have a clinical complete response to preoperative treatment and

avoiding surgery. Long-term results have been reported by Habr-Gama and colleagues¹ on omission of surgery for selected patients with radiological and clinical evidence of complete response after neoadjuvant CRT.

265 patients with distal resectable rectal tumours were treated with preoperative CRT from 1991 to 2002. Radiotherapy was delivered at a dose of 50.4 Gy in 1.8 Gy fractions for six consecutive weeks. Concomitant chemotherapy consisted of fluorouracil (425 mg/m² per day) and folinic acid (20 mg/m² per day) on the first 3 days and last 3 days of radiotherapy. Patients were assessed at 8 weeks (a longer interval than the standard 4–6 weeks) after completion of CRT. 71 patients (26.8%) were deemed to have achieved complete response on clinical and radiological grounds, although MRI was not used (all patients had preoperative CT and endorectal ultrasound was also used in selected cases). These patients with complete clinical response did not have surgery, forming an observation group. All other patients proceeded to surgery.

At a median follow-up of almost 5 years (57.3 months, range 12–156), overall and disease-free survival was 88% and 83% in the resection group and 100% and 92% in the observation group, respectively. Of 71 patients in the observation group about 70% had T3 tumours, 10% T4 tumours, and only 20% had tumours radiologically staged as node positive. 20% of patients had T2N0 disease, all of whom were included based on their requirement for abdominoperineal excision. Only two of these 71 patients had an endoluminal relapse, both of whom were successfully treated. Three patients developed metastatic disease.

This series was updated in 2005 and again in 2006,^{37,38} now extending to 360 patients treated up to 2005, with an additional 28 (now 99 in total) patients classified as having achieved complete clinical response, and, therefore, avoiding surgery. Local recurrence has occurred in three additional patients (five in total) in the CR group, all amenable to salvage surgery, and none of whom have developed further recurrence.

This series predates routine preoperative MRI staging, and the inclusion of T2N0 tumours clearly affects the outcome in a favourable way. Despite these criticisms, however, these results are impressive, and seem to confirm that a non-operative approach might be safe for complete responders to neoadjuvant treatment. Furthermore, patients who would otherwise only have minimum microscopic residual disease at surgery might have an opportunity to achieve complete response with time. These findings suggest that response to preoperative treatment is prognostic, whether surgery is undertaken or not, as has been shown in other studies.^{39,40,41}

Prediction of response to preoperative treatment

At present there is no reliable technique for predicting clinical or pathological complete tumour response after CRT. Limited data exist for each potential modality in

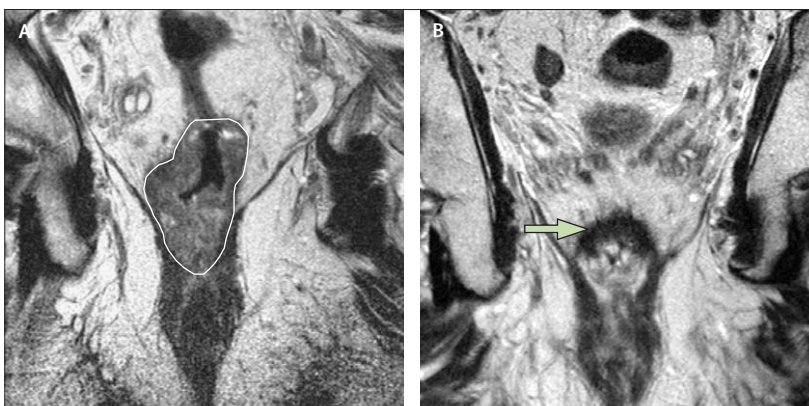


Figure 3: Coronal T2-weighted MRI of T3 tumour

(A) T3 tumour (outlined) infiltrates sphincter. (B) Low-signal-intensity scar (arrow) with obvious tumour regression can be seen 4 weeks after CRT. No evidence of tumour remains.

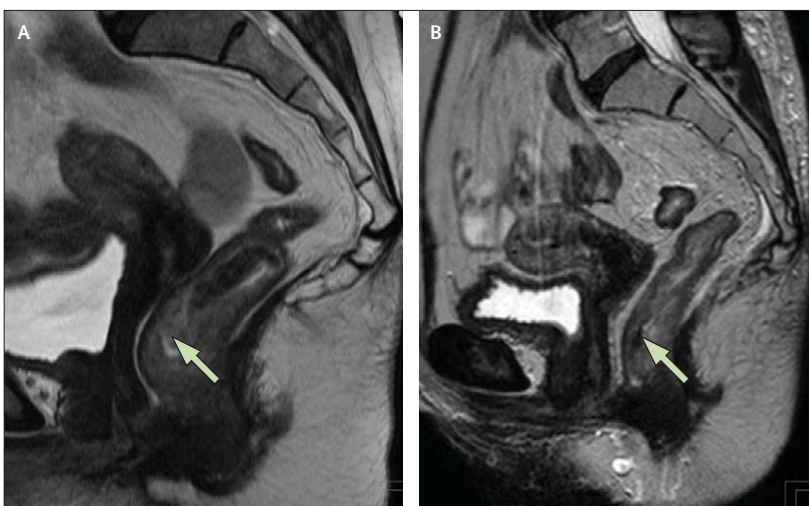


Figure 4: Sagittal T2-weighted MRI of T3 tumour

(A) Bulky T3 low rectal tumour (arrow). (B) Low-signal-intensity scar seen 4 weeks after CRT (arrow). No evidence of tumour remains.

this regard. The greatest challenge for non-operative strategies is patient selection. Therefore, the most promising modalities for prediction of true complete response need to be considered.

MRI

The accuracy of high-resolution MRI in predicting the presence or absence of tumour at the surgical circumferential resection margin of a rectal cancer specimen has been investigated prospectively by the Magnetic Resonance Imaging and Rectal Cancer European Equivalence study group from the Pelican Cancer Foundation (Basingstoke, Hampshire, UK).⁴² 408 patients from 12 colorectal units in four European countries, with all stages of rectal cancer underwent MRI before total mesorectal excision. Specificity for prediction of a clear circumferential resection margin by MRI was 92% (327/354, 95% CI 90–95).

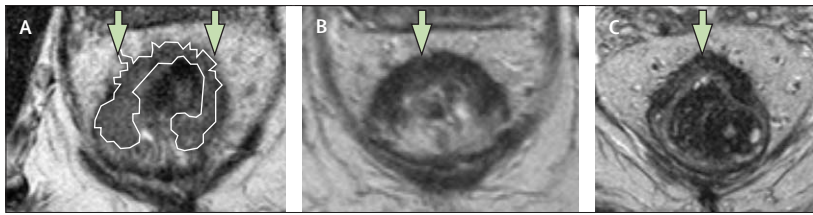


Figure 5: Axial T2-weighted MRI of T3 tumour

(A) T3 tumour (outlined) with anterior infiltration (arrows). (B) Low-signal-intensity scar seen 4 weeks after CRT (arrow). (C) Resolving low-signal-intensity scar with restitution of normal anatomy seen 8 weeks after CRT (arrow).

This is unique data for preoperative imaging and firmly establishes MRI as the modality of choice for preoperative staging before surgery or neoadjuvant treatment. However, the ability of MRI to predict pCR accurately after preoperative CRT has not been established. MRI done 4–6 weeks after the completion of preoperative CRT for locally advanced rectal cancer is rarely normal, even in patients who will show a pCR at surgery. Rather, in patients with an optimum response at MRI, a scar replaces the site of disease, represented by a focal area of low-signal intensity on T2-weighted MR images (figures 3 and 4). The precise cellular composition of such an area of low-signal intensity cannot be known, and a single MRI scan cannot diagnose complete response. However, if surgery is deferred, then the scar can be monitored with serial imaging to exclude any change (figure 5).

PET

Decreases in 18-fluorodeoxyglucose ($[^{18}\text{F}]\text{FDG}$) uptake after completion of CRT have been correlated with long-term outcomes for several malignancies, including Hodgkin's and Non-Hodgkin lymphomas, pancreatic, oesophageal, and head and neck cancers, and germ-cell tumours.

For locally advanced rectal cancer, a number of studies have investigated the importance of $[^{18}\text{F}]\text{FDG}$ uptake before and after CRT. Usually, a second PET is done before surgery 3–5 weeks after completion of CRT, allowing for correlation with pathological findings. A German study⁴³ has shown that $[^{18}\text{F}]\text{FDG}$ -PET is better than CT and MRI (assessed by mean reduction in standardised uptake value [SUV]) for predicting response to preoperative treatment with regional hyperthermia. Furthermore, Italian investigators have correlated percentage SUV decrease with pathological response.⁴⁴ Patients with CR or minimum microscopic disease (12 of 15) had a mean SUV of 2.7 after completion of aggressive preoperative CRT, compared with a value of 5.1 for those with lesser pathological responses. All downstaged and downsized tumours showed a post-treatment SUV of <2.5. Calvo and colleagues⁴⁵ also showed a correlation of tumour downstaging with SUV. In this study, tumours that were downstaged had a post-CRT maximum SUV of 1.9, compared with non-downstaged lesions that had a SUV of 3.3 ($p=0.03$).

These studies seem to correlate metabolic response with pathological response rather than patient outcome. Two studies have also shown statistical significance for prognosis, suggesting that unfavourable tumour biology could be predicted by PET.^{46,47} Post-CRT SUV alone might be better than mean SUV reduction as a prognostic indicator.⁴⁸

PET might also be complimentary to other modalities for follow-up in non-operative strategies, although studies on this up to now have been small. Further work is needed before the effect of PET is known, although inclusion of PET in non-operative protocols might be desirable.³⁷ Habr-Gama and colleagues has now included PET/CT for patients in their series, at baseline, and at 5 and 12 weeks after completion of CRT (Habr-Gama A, Department of Surgery, University of Sao Paulo, Brazil; personal communication).

Digital assessment

Despite the established role of preoperative MRI staging, digital-rectal examination (DRE) remains fundamental in the assessment of palpable rectal cancer, to assess tumour mobility and distal extent. However, DRE seems to have a low positive predictive value in assessing complete response. In the study by Habr-Gama and colleagues,¹ patients with an incomplete clinical response on DRE (residual rectal ulcer) proceeded to surgery, 7% of whom proved to have a pCR. A prospective trial by Guillem and co-workers⁴⁹ is illustrative of this problem. 94 patients with T3, T4, or N1 rectal cancer were examined digitally before CRT, and then preoperatively by the same surgeon. The median interval from completion of CRT to surgery was 48 days. Only 21% (3 of 14) of patients who went on to have pCR were correctly identified by preoperative DRE. The extent of pathological downstaging was underestimated in almost 80% of patients. Abnormalities at DRE before surgery clearly do not preclude a pCR.

Molecular prediction

In view of the fact that clinical and radiological means are currently limited in predicting response to preoperative treatment, molecular markers have been assessed for their predictive value. Studies on P53 using immunohistochemistry (IHC) and single-strand conformational polymorphism analysis have not shown potential.⁵⁰ However, direct sequencing of P53 has shown P53 gene mutations are significantly associated with radioresistance.^{51,52} P21 protein is a key component in the P53 signalling pathway, including in relation to radiotherapy-induced DNA damage. Endogenous P21 expression has been associated with radiotherapy response in IHC studies.^{53–55} Indeed, concentrations of this protein have been shown to change during radiotherapy, with a rise in concentration correlating with a poor prognosis.⁵⁵ Additionally, tumours with a high spontaneous-apoptosis index might have a

corresponding enhanced potential for radiotherapy-induced apoptosis, and such an association has been shown by a number of studies.⁵⁶⁻⁵⁸ Overexpression of cyclo-oxygenase 2,⁵⁰ epidermal growth factor receptor,^{59,60} and growth-hormone receptor⁶¹ are also under investigation and seem promising.

Perhaps the most exciting molecular development has been the use of pretreatment gene-expression profiling. Watanabe and co-workers⁶² achieved an accuracy of 82.4% in predicting radiotherapy response.⁶² By use of microarray technology, 33 genes were identified in which expression varied significantly between responders and non-responders to preoperative radiotherapy, allowing the construction of a predictive model. Ghadimi and colleagues⁶³ used similar techniques for 30 patients in the preoperative group of the CAO/ARO/AIO-94 trial. Analysis of a 54-gene set allowed prediction of tumour response with 78% sensitivity and 86% specificity.⁶³

The prospect of combining clinical, radiological, and molecular information to tailor preoperative treatment for locally advanced rectal cancer is intriguing. Reliance can't yet be placed on molecular data, but as the weight of evidence increases for markers that predict radio-sensitivity, the confidence with which surgery might be omitted for complete responders will increase.

Future directions

With up to 25% of patients having a pCR after neoadjuvant CRT, there is a compelling argument for attempting to avoid surgery in carefully selected groups of patients, especially if surgery involves a permanent colostomy. Although the study by Habr-Gama and colleagues¹ is extremely promising, a systematic prospective trial using modern imaging techniques has not been carried out.

At the Royal Marsden Hospital (Sutton, Surrey, UK) and Pelican Cancer Foundation (Basingstoke, Hampshire, UK), a pilot study has commenced investigating a non-operative approach for complete responders. To our knowledge, this is the first such prospective trial in the world. Patients with locally advanced rectal cancer with a complete response (as evidenced by MRI 4 weeks after completion of preoperative CRT and confirmed by MRI at 8 weeks) will avoid surgery and enter a rigorous programme of MRI, clinical, and endoscopic follow-up. For example, in the first year, after 8-week MRI, patients will undergo 3-monthly MRI, sigmoidoscopy, and clinical assessment. These serial MR images will survey the low-signal-intensity scar seen in complete responders after CRT (figure 5).

Eligible patients will be selected on the basis of baseline MRI findings indicating any of the following: T3 tumours at or below levators; T3 tumours extending ≥ 5 mm into perirectal fat; T4 tumours; presence of extramural venous invasion; or full thickness T2 N0/1/2 tumours needing abdominoperineal excision. Patients with evidence of at least a partial response (defined by

Search strategy and selection criteria

Data for this review were identified by searches of PubMed and references from relevant articles, using the search terms "rectal cancer", "complete response", and "radiotherapy". Abstracts and reports from meetings were included only when they related directly to previously published work. Only papers published in English between 1983 and 2007 were included.

MRI; RECIST criteria⁶⁴) at 4 weeks are eligible once complete response is confirmed by MRI at 8 weeks. Any patient who does not reach complete response, as evidenced by stable persistent disease on MRI, will be urgently referred for surgery. Similarly, evidence of local recurrence at any stage of follow-up will result in urgent surgical referral.

This pilot study, if successful, will aid the formulation of larger-scale trials. Furthermore, it will establish the ability of MRI to predict complete response after pre-operative treatment. As such treatment improves with the introduction of new agents, and the incidence of pCR continues to rise, successful omission of surgery is likely to become increasingly relevant.

Conclusion

The work of Nigro and colleagues⁶⁵ in the 1970s has led to the acceptance of radical CRT as the standard of care for squamous-cell carcinoma of the anus. Thus, the leap of faith needed to believe in non-operative strategies for rectal cancer is significant, although not unprecedented in gastrointestinal oncology. Surgery remains the standard of care after neoadjuvant CRT irrespective of the extent of response, but results from a rigorous controlled trial using modern imaging techniques will be essential to guide oncologists in the selection of appropriate patients for non-operative management of rectal cancer after CRT.

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Conflicts of interest

The authors declared no conflicts of interest.

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