# Do T3 Rectal Cancers Always Need Radiochemotherapy?

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**Abstract**

The limitation of the traditional method of stratifying patients with rectal cancer for prognosis using magnetic resonance imaging (MRI) and computerised tomography (CT)—TNM staging—is that cT3 tumors comprise the vast majority of rectal cancers. There is a wide variability in outcomes for cT3. Despite this observation, many still advocate routine short course preoperative radiotherapy (SCPRT) or chemoradiation (CRT) for all patients staged as cT3N0 regardless of tumour location, proximity to other structures or extent, despite the fact that advances in imaging with MRI now offer the ability to predict potential outcomes in terms of the risk of local and metastatic recurrence for the individual. Preoperative CRT is designed to reduce local recurrence. The majority of local recurrences historically reflected inadequate quality of the mesorectal resection. Currently, optimal quality-controlled surgery in terms of total mesorectal excision (TME) in the trial setting can be associated with much lower local recurrence rates of less than 10 % whether patients receive radiotherapy or not. Because of the high risk of metastatic disease in selected patients, integrating more active chemotherapy is now attractive. Chemoradiotherapy (CRT) achieves shrinkage and sometimes eradication of tumour—i.e. a pathological complete

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response (pCR), and reduces local recurrence, but has no impact on overall survival. CRT also increases surgical morbidity and impacts on anorectal, urinary and sexual function with an increased risk of second malignancies. Hence, the predominant aims of CRT have been to shrink/downstage a tumour to allow an R0 resection to be performed, or to increase the chances of performing sphincter-sparing surgery. However, it remains unclear why shrinkage/downstaging is meaningful to a patient unless the tumour is initially borderline resectable or unresectable (i.e. the CRM is threatened) or the aim is to perform a lesser operation (i.e. sphincter-sparing or local excision) or for organ-sparing, i.e. to avoid surgery altogether. If it is important to shrink the cancer—ie there is a predicted threat to the CRM, then CRT is currently the treatment of choice. If the cancer is resectable and the aim is simply to lower the risk of local recurrence and preoperative CRT does not impact on survival, can CRT be omitted in selected cases? The answer is yes—with the proviso that we are using good quality MRI and the surgeon is performing good quality TME surgery within the mesorectal plane.

## 1 Introduction

Preoperative chemoradiation (CRT) has been the standard of care for patients with clinical stage II and III rectal cancer because of the low rates of local recurrence achieved, acceptable levels of toxicity, and the potential for sphincter preservation compared with postoperative chemoradiation. In contrast, parts of Northern Europe have adopted a blanket approach to short course pre-operative radiotherapy (SCPRT) using 25 Gy over 5 days followed by immediate surgery with the predominant aim of reducing the risk of pelvic recurrence. This strategy of preoperative CRT has been extrapolated from postoperative studies, mainly performed in the US which showed a clear benefit for chemoradiation in terms of local recurrence and survival. The GITSG 7175 trial randomly assigned patients to surgery alone, adjuvant chemotherapy, adjuvant radiation therapy or combined adjuvant chemotherapy and radiation. Since then, no large US phase III trial has included a surgery-alone arm.

However, even with the advantage of accurate histopathogical staging unmodified by neoadjuvant treatment, not all patients benefit from postoperative chemoradiation. Data on 3791 patients within phase III US trials examining postoperative adjuvant treatment in rectal cancer prior to the TME era **(NCCTG 794751, NCCTG 864751, and US GI Intergroup 0114)** (Douglas et al. 1986; O'Connell et al. 1994; Tepper et al. 2002) using pooled analyses show a more complex T and N combined classification can predict outcomes and risk of recurrence: low (T1/2N0), intermediate (T1/2N1, T3N0), moderately high (T1/2N2, T3N1, T4N0) and high (T3N2, T4N1/2). In 1060 patients with pT3N0 tumours classified as intermediate-risk, low rates of local recurrence were

associated recurrence (Gunderson 2004) and there was no improvement in disease-free or overall survival when radiation was added to chemotherapy postoperatively. It should be noted that the majority of patients where radiation was omitted, were treated with surgery and chemotherapy rather than surgery alone. This data led to several prospective studies aimed at determining whether patients with T1/2N1 and T3N0 disease could be treated with surgery and chemotherapy, but without radiation therapy **(NSABP R02)** (Wolmark et al. 2000).

The low risk of local recurrence weakens the view that adjuvant radiotherapy always offers added value to radical surgery and hence is a routine requirement for patients with intermediate-risk tumours (T1/2N1 or T3N0). Many authors have questioned whether selected patients with T1-2, N1-2 or T3N0 lesions have a sufficiently low risk of local and distant relapse with surgery alone, that they could avoid radiotherapy (Willett 1999).

Recent improvements in the quality of surgery, MRI and pathogical reporting of the operative specimen, also mean the time has come to question both these approaches (CRT or SCPRT).

The majority of the rectum lies below the peritoneal reflection and has no serosa, allowing tumour growth to extend deeply into peri-rectal fat. Historically, high rates of local pelvic recurrence following radical surgery were described. However, surgical practice has evolved, and the technique of meticulous mesorectal dissection where the surgeon removes all of the surrounding mesorectal fat using sharp dissection in a neat anatomical package is associated with much lower rates of local recurrence and improved survival. With expert total mesorectal excision (TME) consistently performed in specialist centres, metastatic disease is now the predominant problem (Cecil et al. 2004), reflecting the likely presence of distant micrometastases at diagnosis, rather than inadequate surgery. It is true that old meta-analyses have shown that preoperative adjuvant radiotherapy reduces local recurrence rates by almost 50 % and overall mortality by 2–10 %. However, the local recurrence rates were very high in the region of 15–30 %, and importantly the trials included in these meta-analyses all use patient data from long before the introduction of TME surgery, which questions their current relevance.

Conventional therapies for patients with locally advanced rectal cancer appear to have reached a therapeutic plateau, as none of the recent phase III studies investigating the use of radiotherapy or chemoradiation have improved overall survival (OS). This may also reflect the difficulty of performing large scale multicentre studies, where the quality assurance is inevitably more variable.

In addition to the risk of a local recurrence, 10–40 % of patients require extensive surgical procedures, which lead to a permanent stoma. Surgeons will strive to preserve the anal sphincter, but it has been reported that in the United Kingdom that there is a wide variation in the proportion of patients undergoing an abdomino-perineal excision of the rectum (APER) (Morris et al. 2008)—which may either reflect skills and training or the variability in the use of radiotherapy and concerns regarding function after the combination of preoperative radiotherapy and ultra low anterior resection.

In general, we have focussed on avoiding local recurrence and facilitating sphincter sparing in our phase III trials, hoping that improvements in survival would automatically follow if the primary endpoints were achieved. Sadly this has not been the case. Trials suggest that in resectable cancers, where the preoperative MRI predicts the circumferential resection margin (CRM) is not potentially involved, then SCPRT and CRT are equivalent in terms of outcomes such as local recurrence, DFS and OS (Bujko et al. 2006; Ngan 2010). However, none of the trials of radiotherapy alone (Peeters et al. 2007; Sebag-Montefiore et al. 2009) or chemoradiation published in the last decade have impacted on DFS or OS (Sauer et al. 2004; Bosset et al. 2006; Gerard et al. 2006; Roh et al. 2009). Local recurrence is now sufficiently low that (unlike in breast cancer) it fails to impact on overall survival. Alternatively, either the populations in these trials are too low risk to benefit or the inadequacy of the systemic therapy within current chemoradiation schedules may help to explain this finding.

Fluoropyrimidine-based CRT does not employ systemic doses of chemotherapy and delays the integration of adjuvant chemotherapy. Enthusiasm has been stimulated by the efficacy of oxaliplatin in dealing with distant micro-metastases in the adjuvant setting in colon cancer (Kuebler et al. 2007; Andre et al. 2009). However, results of trials using oxaliplatin as a radiosensitizer alone have not been shown to change early outcome measures rate (Aschele et al. 2011; Gerard et al. 2010; Gerard et al. 2012; Roh et al. 2011; Rödel et al. 2012; Schmoll et al. 2013) and toxicity is substantial. The current therapeutic challenge is to optimize all our available non-operative strategies by effective cytotoxic chemotherapy at systemic doses. Incorporating new agents into current therapeutic regimens to reduce the burden of metastases is a priority for research.

In contrast, for more locally advanced cases, where the CRM is breached or threatened according to the MRI, the integration of more active chemotherapy and biological agents into chemoradiation is an attractive strategy. There is an obvious need to improve response to downsize the tumour to achieve a curative resection, and there is a high risk of metastases. In patients where even technically optimised surgery is unlikely to achieve a curative resection—5FU-based chemoradiation has been shown to have a statistically significant effect on resectability and relapse free survival (Frykholm et al. 2001; Braendengen et al. 2008). However, these trials have been underpowered to show a benefit in terms of overall survival. At the time of diagnosis between 20 and 25 % of patients with rectal cancer will be found to have overt metastatic disease, and a further 30–40 % will subsequently develop metastases.

However, the rationale for CRT has been overcalled because of inflated assessments of what is ‘locally advanced disease’, which is facilitated by ultrasound-based rather than MRI-based staging. Hence all cT3 are often considered LARC. There is also a tendency to overstage patients radiologically if the CRM is predicted to be threatened by 2 mm or even 3 mm where 1 mm is sufficient, and the clinical stage migration of cT2 to cT3a engendered by a traditionally cautious approach by radiologists. The delivery of CRT is perpetuated by the reluctance of surgeons to risk a positive margin or the possibility of local recurrence without the safety net of pelvic radiotherapy.

## 2 Imaging

Initial staging with MRI now offers a high degree of accuracy in predicting peritoneal involvement in upper rectal cancer above the peritoneal reflection, and the depth of extramural spread and CRM involvement in mid and low rectal cancers. In low rectal cancers, the mesorectum thins markedly at the level of levator ani—especially anteriorly in relation to prostate, and predicting potential CRM involvement becomes more difficult.

Recent advances in imaging particularly in terms of the precision available with MRI offer the ability to predict potential outcomes in terms of the risk of local and metastatic recurrence from a range of structural and other features (such as extramural venous invasion, nodal involvement inside and outside the mesorectal fascia, and depth of penetration through the muscularis propria).

The risk of local (pelvic) relapse reflects the degree of tumour extension beyond the rectal wall and to nodal spread. T3c and T3d rectal cancers have markedly worse progression-free and cancer-specific survival compared to T3a and T3b (Pollheimer et al. 2010). This extension can be accurately assessed by MRI within 0.5 mm of tolerance (Mercury 2007).

High spatial resolution coronal imaging also defines the levator muscles, the sphincter complex and intersphincteric plane with sufficient accuracy to allow us to plan the most appropriate plane of surgery (standard TME surgery, intersphincteric resection, APER, or Extralevator abdominoperineal resection, CRT and local excision, TEM). If we can make decisions like this with widely different impacts on QOL, based on MRI appearenaces, then we should also be taking into account the features which predict the risk of local versus metastatic disease.

## 3 Local Recurrence

The majority of local recurrences historically reflected inadequate mesorectal resection (Syk et al. 2008), which is a common finding on postoperative MRI after partial mesorectal excision (Bondeven et al. 2013). Currently, optimal quality-controlled surgery in terms of TME in the trial setting can be associated with local recurrence rates of less than 10 % whether patients receive radiotherapy or not (Quirke et al. 2009). Factors which compromise the performance of good quality TME are well recognised and include patient and disease—related aspects and the surgeon's case volume (Garlipp et al. 2012).

One reason that local recurrence occurs after potentially curative resection is explained by the work of Quirke and colleagues. The presence of microscopic tumour cells within one millimetre of the radial or CRM is clearly demonstrated to be associated with a very high rate of local recurrence and poor survival. High-resolution pelvic MRI using surface phased array coils is now routinely applied in the UK and much of Europe as a preoperative staging and selection tool for the use of neoadjuvant radiation. MRI strongly predicts the likelihood of involvement of

the CRM particularly in the mid-rectum, involvement of the levators in the low rectum and the extramural depth of invasion. The risks of local failure are much lower for cancers in the upper rectum. This MRI preoperative assessment can identify patients at risk of the surgeon being unable to achieve an R0 resection (MERCURY 2007). The accuracy of predicting tumour extent beyond the muscularis propria was within 0.5 mm tolerance in the mid/upper rectum, and suggests MRI can accurately predict ultimate outcome. MRI can also accurately measure the distance between the anorectal junction and/or and the distal part of the tumour and the luminal length of the tumour. However, MRI, multisclice CT and ERUS all remain inadequately accurate to detect involved or uninvolved lymph nodes despite specific imaging features such as size $\geq$8 mm/round/heterogenous/irregular in nodal border. Current studies have also failed to confirm that FDG-PET has improved the accuracy of nodal staging.

Location of the primary tumor (anterior and low confer more risk) and site within the rectum (upper, middle and lower) is also important. MRI is increasingly influencing both the rationale for neoadjuvant radiotherapy, and the design of current trials. Other pathological factors which increase the risk of recurrence include T4 tumours, nodal involvement, extramural vascular invasion, perineural invasion and extranodal deposits (Kusters et al. 2010). Some of these can be identified also on preoperative MRI. Other recognised clinical, individual or social factors that influence the development of recurrence include surgeon variability, grade and sex, and BMI.

However, our sophistication in making decisions and our categorisation of risk for these tumours has not kept pace, since about 65–70 % of rectal cancers are classified as locally advanced rectal cancer (LARC).

The most recent update of the Dutch TME trial in rectal cancer (Van Gijn et al. 2011) reported a 10 year local recurrence cumulative incidence of 5 % in the group assigned to short course preoperative radiotherapy (SCPRT) (5X5 Gy) versus 11 % in the surgery alone group ($P < 0.001$). This 50 % reduction in local recurrence is maintained long-term, and in a non-protocolised subset analysis of 435 TNM stage III patients with a negative CRM, i.e. 23 % of the total population, preoperative radiotherapy appears to improve 10 year OS from 40 to 50 % ($p = 0.032$). However, this finding does not take into account the quality of the mesorectal excision. Node positive patients with defects in the mesorectum are likely to be at high risk of local recurrence, whereas complete mesorectal excision will lead to local recurrence overall in the range 7–8 % (Quirke et al. 2009).

Yet, for all groups the results of the Dutch trial do not show a difference in OS (Van Gijn et al. 2011), which implies that either the result has arisen by chance as a type I error or some population groups within the trial (? node negative) are disadvantaged in terms of survival by radiotherapy.

## 4 Late Effects of Radiotherapy

There are significant late-effects from pelvic radiotherapy on anorectal, urinary and sexual function (Peeters et al. 2005; Lange et al. 2007), and a increased risk of second malignancies after 10 years (Birgisson et al. 2005; Van Gijn et al. 2011). Small bowel tolerance is a dose-limiting factor. A Cochrane review (Pachler et al. 2012) reported that CRT negatively affect the patient's quality of life in rectal cancer and prompts the need for larger and better designed future prospective studies to examine whether a colostomy is associated with worse QOL.

Effects on sexual functioning (Marijnen et al. 2005), urinary incontinence (Pollack et al. 2006), faecal incontinence (Lange et al. 2007), have been documented after SCPRT. These complications depend on the size of the radiation field, shielding, the overall treatment time, the fraction size and total dose. Mature results of the Swedish Rectal Cancer Trial confirm problems after RT particularly bowel obstruction and abdominal pain (Birgisson et al. 2006). There are also unexplained late cardiac effects (Pollack et al. 2006) and insufficiency fractures in the pelvis (Herman et al. 2009). In addition, in the Dutch TME study deaths from second malignancy were higher in the RT arm than the TME alone arm (13.7 vs. 9.4 %) (Van Gijn et al. 2011). Given this finding is seen after only 11.6 years follow-up—this difference may widen further after 15–25 years. As follow-up in the majority of studies is generally short, the risks of these late effects are likely to be underestimated. It is unclear how much these effects are highlighted in the consent process for radiotherapy. In contrast to radiotherapy, the side effects of chemotherapy are usually short-term, although the neuropathy from oxaliplatin may be permanent.

## 5 Postoperative Adjuvant Chemotherapy

Because of the high risk of metastatic disease, integrating more active chemotherapy is attractive, and enthusiasm has been stimulated by the efficacy of oxaliplatin in dealing with distant micro-metastases in the adjuvant setting in colon cancer (Kuebler et al. 2007; Andre et al. 2009) although patients with rectal cancer were excluded as ineligible. The possible options for systemic chemotherapy option have expanded, but postoperative adjuvant chemotherapy remains only partially effective, and toxicity (particularly with oxaliplatin) is substantial. The current therapeutic challenge is to optimise all our available non-operative strategies by effective cytotoxic chemotherapy at systemic doses. Incorporating new agents into current therapeutic regimens to reduce the burden of metastases is a priority for research.

Compliance to postoperative chemotherapy following chemoradiation is poor. Neoadjuvant chemotherapy (NACT) offers an alternative strategy. At least 20–25 % of patients in whom chemotherapy with 5FU might be considered may not be sufficiently fit or decline treatment (Sauer et al. 2004; Bosset et al. 2006; Gerard et al. 2006). Compliance to additional postoperative oxaliplatin appears even worse (Rödel et al. 2007).

## 6 Does Chemotherapy Impact on Local Recurrence?

Systemic chemotherapy has been shown to enhance local control with radiation (Bosset et al. 2006; Bosset et al. 2013; Gerard et al. 2006) after radiation (Bosset et al. 2006; Bosset et al. 2013) or without radiation (Akasu et al. 2006).

In a study of patients with curatively resected stage III rectal cancer, who underwent TME with selective lateral pelvic lymphadenectomy, patients were randomised postoperatively to receive either oral uracil-tegafur (400 mg/m2 tegafur per day) for 12 months or no treatment. The rates of overall local recurrence were 5.8 % (8/139) for the uracil–tegafur group and 9.6 % (13/135) for the surgery-alone group (Akasu et al. 2006). If radiation therapy does not improve survival and systemic chemotherapy enhances local control with or without radiation, and surgical salvage is possible in 50 % if sequential MRIs are performed, then radiation may not always be required. Currently, although local recurrence does increase the risk of distant metastases, local recurrence is reduced to single figures and salvage surgery is effective in more than 50 %.

A recent small prospective trial at Memorial Sloan-Kettering Cancer Center (Schrag et al. 2014) in 32 rectal cancer patients (22 with clinically staged node-positive disease) evaluated the replacement of standard preoperative fluorouracil-based chemoradiation with neoadjuvant FOLFOX (six cycles) and bevacizumab (four cycles) and no radiation. In the 30 patients who completed this neoadjuvant therapy and had a curative TME resection, eight patients (27 %) achieved a pathologic complete response (PCR), and 0/32 patients suffered a local recurrence.

## 7 Are There Patients for Whom Neoadjuvant Chemotherapy Is an Alternative?

There is clearly a high risk of metastatic disease in locally advanced rectal cancer, yet systemically active doses of chemotherapy are not delivered in CRT schedules, and compliance to postoperative adjuvant chemotherapy is generally poor. Extrapolating from positive studies in colon cancer, many oncologists are encouraged to use a FOLFOX regimen as postoperative chemotherapy for stage III patients after chemoradiation. The optimal number of cycles of such treatment has not been determined. Hence, some groups have extrapolated even further and added chemotherapy either prior to CRT, when compliance to chemotherapy is high (Fernandez-Martos et al. 2010; Fernandez-Martos et al. 2011), or following chemoradiation to increase the response rate (Garcia-Aguilar et al. 2011). Some groups have suggested that this strategy leads to excellent long-term results, but raise concerns for a high early death rate (Chua et al. 2010). Others have proposed NACT alone without radiation (Glynne-Jones et al. 2012).

## 8 The Importance of Good Surgery

Historically, the majority of local recurrences reflected inadequate mesorectal resection (Syk et al. 2008) as in a series of 2,315 patients operated on by surgeons trained to perform TME; on MRI there was evidence of residual mesorectal tissue in 50/99 local recurrences. Also, unintentional persistent residual mesorectal tissue (defined as mesorectum above the level of the anastomosis) perpendicular to the bowel was observed in a study on postoperative MRI in 54 (40 %) of 136 patients—particularly after partial mesorectal excision in upper rectal cancers (Bondeven et al. 2013). In the Dutch TME study only mobile tumours were selected as eligible, and the local recurrence rates appear too high to validate the claim that the whole series represents 'standardised TME surgery'.

Some surgical authors have stressed the importance of careful dissection particularly in the posterior aspect of a TME specimen as there is a higher prevalence of lymph nodes in this position (Perez et al. 2008), and it is easy to come out of the appropriate surgical plane. It is acknowledged that the quality of TME can be influenced both by the patient's age, morphology and morbidity as well as disease-related factors (site, position and stage) as well as the surgeon's case volume (Garlipp et al. 2012).

The quality of radical surgery has an independent prognostic factor, which may impact on long-term outcomes. Hermanek, Quirke and Nagtegaal have promoted the importance of assessing the quality of the mesorectum in the surgical specimen and recording by means of a photograph. This classification derives from the original findings from Hermanek and Quirke with three grades based on the completeness of the removal of the mesorectum.

A TME specimen ideally should have a smooth surface, without incisions or tearing, as an indication of successful surgery. 'Coning' is a tendency for the surgeon to cut inwards towards the central tube of the rectum during distal dissection, rather than staying outside the visceral mesorectal fascia, which gives the specimen a tapered, conical appearance. This observed feature is an indication of suboptimal surgical quality (Hermanek and Heald Hermanek and Heald 2004).

Two trials—the CLASSICC study of the Medical Research Council in the United Kingdom and the Dutch TME trial have originally defined a protocol to assess the quality of surgery. This classification has been utilised in the MERCURY study and the CRO7 study (Quirke et al. 2009). Multivariate analysis will need to be validated in future randomised studies.

## 9 Can Radiotherapy Be Omitted?

Several groups have explored omitting radiotherapy when MRI suggests the tumour is easily resectable. This omission does not appear to have increased the local recurrence rate (Taylor et al. 2011; Frasson et al. 2011; Mathis et al. 2012). It seems clear that the surgeon needs to expect to be able to perform an optimal plane

**Table 1** Histopathological grading of the quality and completeness of the mesorectum in a total mesorectal excision specimen

| | Mesorectum | Defects | Coning | CRM |
|---|---|---|---|---|
| Complete | Intact, smooth | Not defects deeper than 5 mm | None | Smooth, regular |
| Nearly complete | Moderate bulk, but irregular | No visible muscularis propria | Moderate | Irregular |
| Incomplete | Little bulk and very irregular | Down to muscularis propria | Moderate–marked | Irregular |

of surgery i.e. to achieve a surgical specimen with an intact mesorectum displaying only minor irregularities over a smooth mesorectal surface; with no defect deeper than 5 mm; with no coning; and with a smooth CRM on slicing (Quirke et al. 2009) (Table 1).

Three feasibility/retrospective studies of NACT alone without radiation (Cercek et al. 2010; Ishii et al. 2010; Fernandez-Martos et al. 2012; Schrag et al. 2014) used FOLFOX plus/minus bevacizumab (Table 2). The pCR rate after chemotherapy alone varied from to 7–35 %, but as small non-randomised studies are unable to show an impact on metastatic disease. The studies are too small and not sufficiently mature to assess the local recurrence rate. However, the proof of principle has given rise to many current studies exploring NACT (Table 3).

## 10 Are There Clearly Distinguishable Groups Who Do not Need RT?

Accurate information on primary tumour local extension, precise location, potential nodal-stage, potential CRM involvement and extra-mural venous invasion is essential for defining the optimum treatment strategy on an individual basis. Currently, the definition of locally advanced rectal cancer is variable from unit to unit. Currently, in the UK many MDTS categorise patients into 'The good, the bad and the ugly', which allows definition of three different settings where preoperative neoadjuvant treatment may or may not be required. For clinically unresectable cancers or where MRI shows a threatened/breached CRM (10–15 % of cases), or in cancers which require surgical resection beyond the conventional TME plane, then radiation as a component of CRT is clearly necessary. In contrast, early cT1/T2 tumours are not usually treated with radiotherapy because of the low risk of local recurrence. The problem with these above systems is that the intermediate risk represents a wide spectrum, with variable behaviour and should be defined more accurately with further risk groupings. Since in the trials about 50 % of patients are low rectal cancer within 5 cms of the anal margin, probably more than 50 % are stage 2 and up to 30 % are T2 initially. A T3 subclassification has been proposed in 2001 by Merkel from the Erlangen group, who suggested the

**Table 2** Phase I/II studies of neoadjuvant chemotherapy without radiation

| | No of pts* | Eligibility | Induction Chemotherapy | Toxicity | PCR** | T Mic*** | R0 | Late outcome |
|---|---|---|---|---|---|---|---|---|
| Ishii 2010 | 26 | cT3/T4 N0–2 | Irinotecan (80 mg/m$^2$), FUFA days 1, 8, and 15 for 4 weeks | Not stated | 1/15 (7 %) | Not stated | Not stated | 5 year RFS 74 % OS 84 % |
| Schrag 2010 | 31 | Clinical stage II–III (but not T4) | FOLFOXbevacizumab (6 cycles bev 1–4) | 2 pts withdrawn (angina arrhythmia) | 8/29 (27 %) | Not stated | 29/29 (100 %) | No data |
| Cercek 2010 | 20 | RT contraindicated or presence of synchronous metastases | 6 pts FOLFOX 14 pts FOLFOX + Bev | Not stated | 7/20 (35 %) 2/6 (33 %) rectal cancer without metastases | Not stated | Not stated | No data |

* number entering study
** number having had surgery
*** using regression grading not yp

**Table 3** Trials of neoadjuvant chemotherapy in progress

| Study (Reference) | Pre-operative treatment | Entry Criteria | Status | RT/CRT | Comments |
|---|---|---|---|---|---|
| Phase III trials | | | | | |
| GEMCAD (Fernandez-Martos 2010) 41 patients | Capecitabine/oxaliplatin + bevacizumab 3 cycles then capox = total 4 cycles | MRI defined entry | Recruiting | Selective CRT according to response | Primary endpoint: response rate (RECIST) |
| RAPIDO Phase III EudraCT number 2010-023957-12 885 patients | SCPRT (5 × 5 Gy) followed by Oxaliplatin/capectabine 6 cycles versus Control Capecitabine +CRT | MRI defined entry | Yet to open | CRT 50.4 Gy/28# with capecitabine | Primary endpoint: 3 year DFS |
| Polish study EGBRJ 0109 NCT00833131 540 patients | SCPRT (5 × 5 Gy) followed by FOLFOX (3 cycles) then surgery versus Versus 5FU/capecitabine CRT (50 Gy) as control | Unresectable rectal cancer | Recruiting | SCPRT versus CRT | Primary endpoint: the rate of R0 resection |
| | Randomised phase II trials | | | | |
| BACCHUS NCRI Randomised phase II 60 patients | FOLFOX +bevacizumab for 5 courses, then final FOLFOX then surgery Versus FOLFOXIRI bevacizumab for 5 courses, then final FOLFOXIRI then surgery | MRI defined entry | Yet to open | SCPRT or CRT only for progression/lack of response | Primary endpoint: pCR |
| randomised phase II GRECCAR 4 150 patients | FOLFIRINOX 4–8 weeks then reassess/randomised according to response If good cap 50 Gy versus surgery If poor cap 50 Gy versus cap 60 Gy | MRI defined entry | ?started | If good cap 50 Gy versus surgery If poor cap 50 Gy versus cap 60 Gy | Primary endpoint: %R0 |

(continued)

**Table 3** (continued)

| Study (Reference) | Pre-operative treatment | Entry Criteria | Status | RT/CRT | Comments |
|---|---|---|---|---|---|
| French phase II<br>NCT00865189<br>91 patients | FOLFOX +bevacizumab<br>for 6 courses then CRT(with bevacizumab/ 5FU) versus CRT alone | Not MRI | Ongoing not recruiting | | Primary endpoint: pCR |
| Chinese Randomised phase II<br>NCT01211210<br>495 patients | FOLFOX (4 cycles) then surgery versus FOLFOX CRT<br>Versus 5FU CRT (control) | Not MRI | Recruiting | | Primary endpoint 3 year DFS |
| SWOG study<br>NCT00070434<br>Up to 65 patients | Multiple regimens | T4 rectal cancer | Ongoing not recruiting | CRT with cape | Primary endpoint: response |

subdivision of T3 into T3a < 5 mm and T3b > 5 mm (Merkel et al. 2001). The Mercury Study Group extended this subclassification further into four groups: 'a' (<1 mm outside the wall), 'b' (1–5 mm), 'c' (5–15 mm) and 'd' (>15 mm) (MERCURY 2007; Smith and Brown 2008). Distinction between cT2 and cT3a remains difficult, but may be less relevant to outcome because the Erlangen data suggests that prognosis is not significantly different for these two groups. MRI can define macroscopic extramural vascular invasion (EMVI), which occurs in about 40 % of patients (Smith et al. 2008). This feature predicts for systemic failure with good concordance between MRI EMVI and eventual pathology EMVI prognostic outcome (Dirschmid et al. 1996; Sternberg et al. 2002), suggesting that patients with macroscopic EMVI have only a 30 % 3 year disease free survival.

A structure which defines three risk groups within the broad intermediate risk category, with low risk of local recurrence/low risk of metastatic disease, low risk of local recurrence/high risk of metastatic disease, high risk of local recurrence/low risk of metastatic disease, high risk of local recurrence/high risk of metastatic disease is therefore proposed (Table 4).

Chemotherapy prior to CRT or SCPRT does not compromise the delivery CRT, but has not increased pCR rates, R0-resection rate, improved DFS or reduced metastases. There is significant late morbidity from pelvic radiotherapy and a doubling of the risk of second malignancy. Hence, NACT alone without radiotherapy could be explored compared with SCPRT or CRT in selected patients with resectable rectal cancer showing adverse features (extramural vascular invasion etc.) in a future research programme.

## 11 Biomarkers

There has also been a recent focus on predictive and prognostic molecular biomarkers from the longstanding orthodoxy of carcinoembryonic antigen (CEA) through Kras and Nras mutations, to insight regarding phosphoinositide 3-kinase (PI3 K) mutations and wild type p53. Although none of these novel strategies have been validated, they allow us to hope that we can select and stratify patients according to their different molecular and imaging patterns. This knowledge select patients for certain treatments and may also spare other patients from treatment, which is unlikely to be effective. Criteria are therefore emerging, which suggest a possible future role for individually tailored therapy.

## 12 The Future

A multi-institutional phase II/III randomised, prospective trial (NCCTG-N1048, NCT01515787) currently compares neoadjuvant FOLFOX with selective use of chemoradiation. The study randomises rectal cancer patients with low risk cT1/2N1, cT3N0 and cT3N1 disease, with lesions located 5–12 cm from the anal verge

**Table 4** Proposed mid rectal cancer risk categorisation based on MRI and clinical risk factors

| Low risk | Intermediate risk | | | High risk |
|---|---|---|---|---|
| Low risk local recurrence/low risk metastases | Low risk local recurrence/ moderate risk metastases | Moderate risk of local recurrence/ high risk metastases | High risk of local recurrence/higher risk metastases | High risk local recurrence/ high risk metastases |
| MRI cT2/T3a/ T3b < 4 mm extension into muscularis propria CRM not threatened (predicted ≥2 mm) cN0 CT M0 | MRI cT3b > 4 mm extension into muscularis propria CRM not threatened (predicted ≥2 mm) cN1, CT M0 | MRI cT3b > 4 mm cT3c, cN2, V2 CRM not threatened (predicted ≥2 mm) CT M0 | MRI cT3d, T4a (resectable) CRM not threatened (predicted ≥2 mm) CT M0 | MRI cTany extension into muscularis propria, T4b CRM breached or threatened (predicted <1 mm) CT M0 ? Mucinous |
| Clinical factors | Obesity<br>Male/with anterior tumours<br>Narrow pelvis<br>Previous pelvic surgery<br>Large bulky tumour<br>Sepsis/fistula/perforation | | | |
| NICE guidelines low risk +, but does not include T3b < 4 mm | *UK Nice guidelines intermediate risk*<br>any cT3b or greater, in which the potential surgical margin is not threatened *or*<br>any suspicious lymph node not threatening the surgical resection margin *or*<br>the presence of extramural vascular invasion | | | NICE guidelines high risk a threatened (<1 mm) or breached resection margin **or** low tumours encroaching onto inter-sphincteric plane or levator involvement |
| NICE<br>do not give RT | *Nice guidelines (UK)*<br>SCPRT or CRT | | | NICE<br>CRT recommended |
| Potential MRI directed recommendations | | | | |
| No requirement for preop radiotherapy Immediate surgery | If surgeon convinced able to perform R0 resection and good quality in mesorectal plane could omit RT | SCPRT or CRT depending on whether shrinkage of tumour required or Neoadjuvant chemotherapy alone | SCPRT or CRT depending on whether shrinkage of tumour required or Neoadjuvant chemotherapy alone | Requires Chemoradiation (CRT) |

and amenable to sphincter-preserving surgery, to either the standard of preoperative 5-fluorouracil /capecitabine-based chemoradiation, followed by TME and FOLFOX (eight cycles) or to omot radiation and receive neoadjuvant FOLFOX (six cycles). If clinical response ($\geq$20 %) is observed at restaging, then patients undergo surgical resection followed by adjuvant FOLFOX (six cycles). Only those patients with histologically CRM undergo chemoradiation, because of their increased risk of local recurrence. In contrast, if clinical response is <20 %, patients are administered standard combined modality therapy followed by surgery and adjuvant FOLFOX (two additional cycles).

Similarly in the UK, the ongoing BACCHUS randomised phase II study (registered at ClinicalTrials.gov as NCT01650428) evaluates the efficacy of FOLFOXIRI and bevacizumab compared to FOLFOX and bevacizumab omitting radiotherapy. The study aims to examine whether intensive NACT will deliver pathological responses of the primary tumour at least equivalent to CRT as well as reducing the risk of local recurrence and metastasis. If this triple regimen is feasible, effective and tolerable, it would be suitable for testing as the novel arm against the current standards of SCPRT (5 $\times$ 5 Gy) and/or 5FU-based CRT in a future randomised phase III trial.

## 13 Conclusion

To achieve pelvic control the surgeon needs an R0 resection. Hence, preoperative CRT is an important component of the multimodality treatment of rectal cancer if the CRM is threatened. Pelvic failure gives rise to awful and debilitating symptoms, including intractable pain and intestinal obstruction, and a very poor quality of life. However, for less advanced cases, an R0 resection may be more straightforward, and the risk of metastatic disease now predominates over the risk of local recurrence. It is difficult to understand how monolithic approaches, established by studies conducted more than a decade ago, with none of the modern amenities currently available still drive some to apply the same schedule of SCPRT or CRT for all patients with cT3No resectable rectal cancer irrespective of tumour position, extent and treatment goal (Sebag-Montefiore et al. 2009).

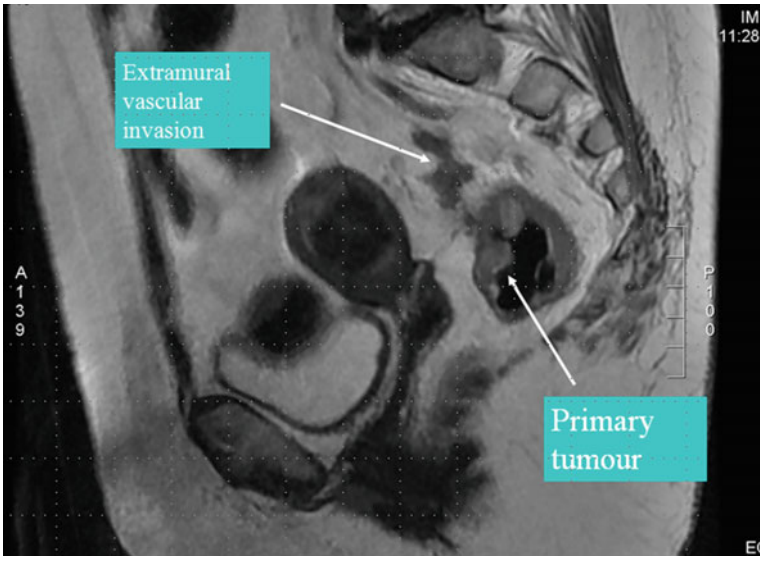
Modern MRI can define patients with a high risk of metastases (EMVI, T3c and T3d)—particularly in the mid rectum. This high risk of metastatic disease means that the use of chemotherapy at systemically-effective doses would seem essential if we are to improve survival in patients with locally advanced rectal cancer. The use of chemoradiation has compromised the integration of full systemic doses and the uptake of postoperative chemotherapy. In contrast NACT has been shown to allow full delivery of chemotherapy in systemic doses and an appropriate intensity without compromising surgery.

The current term of ‘locally advanced rectal cancer’ or ‘T3 /T4’ rectal cancer includes a large proportion of patients who either do not need radiotherapy or equally are not going to benefit in a significant way from chemotherapy, using

analogies of the benefit of chemotherapy in low risk stage II colon cancer. We need a new description /term for locally advanced rectal cancer, which provides an effective risk categorisation. What is the predominant risk? Local recurrence or metastatic disease? A proposal is tabled in this chapter.

All patients with cT3 rectal cancer should be discussed in a well functioning MDT. Patients should be categorised according to clinical stage TNM, site in the rectum, quadrant, and accurate localization in respect to the mesorectal fascia and levators. Other factors, such as cN-stage, and vascular and nerve invasion are important histologically although the prediction of nodal involvement is poor at present and only macroscopic/gross vascular invasion can be imaged at present.

So, can we not do without radiotherapy if the CRM is not threatened? This may be more easily accepted in the upper and mid rectal cancers than in low cancers. But if we still cling to the notion that RT is needed in all cases in the modern TME era, have we simply turned full circle and are back to advocating preoperative radiotherapy to compensate for poor surgical technique? Or can we accept that if we see the surgeon performing good quality surgery in 80–90 % of his specimens within the mesorectal plane and the MRI suggests clear margins, that the benefit from CRT is marginal.



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