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GASTROINTESTINAL CANCERS (L SALTZ, SECTION EDITOR)

Toward the Non-surgical Management of Locally Advanced Rectal Cancer

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Abstract Neoadjuvant short-course radiotherapy and long-course chemoradiation (CRT) reduce local recurrence rates when compared to surgery alone and remain widely accepted as standard of care for patients with locally advanced rectal cancer. However, surgery is not without complications and a non-surgical approach in carefully selected patients warrants evaluation. A pathological complete response to CRT is associated with a significant improvement in survival and it has been suggested that a longer time interval between the completion of CRT and surgery increases tumor downstaging. Intensification of neoadjuvant treatment regimens to increase tumor downstaging has been evaluated in a number of clinical trials and more recently the introduction of neoadjuvant chemotherapy prior to CRT has demonstrated high rates of radiological tumor regression. Careful selection of patients using high-resolution MRI may allow a non-surgical approach in a subgroup of patients achieving a complete response to neoadjuvant therapies after an adequate time period. Clearly this needs prospective evaluation within a clinical trial setting, incorporating modern imaging techniques, and tissue biomarkers to allow accurate prediction and assessment of response.

Keywords Rectal cancer · Neoadjuvant · Short course radiotherapy · Long course chemoradiation · Surgery · Total mesorectal excision · Pathological complete response · Sphincter sparing · Tumor regression · Local control · Biomarkers · Gastrointestinal cancers

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Introduction

Rectal cancer remains a significant problem worldwide accounting for 25% of all colorectal cancer cases [1]. In the majority of cases (~75%) the disease is localized to the primary site with no evidence of distant spread and in these patients surgical resection currently remains the cornerstone of treatment. The surgical technique is dependent on the position and stage of the tumor and is distinct to that performed for colon tumors. Transanal excision of rectal cancer is possible for selected patients with early-stage cancers. The degree of submucosal (SM) invasion influences the risk of nodal metastases, increasing from 0%–3% for SM1 to 8%–10% for SM2 and 23%–25% for SM3. [2] Therefore local excision is only appropriate for T1 SM1/SM2 tumors that are well-moderately differentiated with no clinical or radiological evidence of lymphadenopathy [3]. Local excision of T1 SM3 or T2 tumors is associated with higher rates of local recurrence when compared to traditional surgical approaches [4], highlighting the need for careful patient selection. Local excision of T1/T2 lesions followed by chemoradiation has been evaluated in a number of studies, however is not equivalent to radical surgery [5–8].

For those with locally advanced tumors, total mesorectal excision (TME) is the established standard of care [9•, 10]. The position and size of the tumor will influence whether the patient requires an abdominoperineal resection (APR), resulting in a permanent stoma or an anterior-resection enabling sphincter preservation. Preservation of both anal and rectal function in treatment of rectal cancer is highly

preferred by patients [11] and anterior resections are associated with less morbidity than APR [12–14]. Surgical resection is not without complications including the risk of anastomotic leak, wound infections, and dehiscence and even patients undergoing sphincter-sparing surgery may have altered continence after surgery. Other postoperative disturbances in function include transient urinary dysfunction secondary to weakening of the detrusor muscle and sexual dysfunction [3].

Histological involvement of the circumferential margin (CRM) is a powerful predictor of local recurrence, distant metastases, and survival [15•] and high-resolution MRI allows identification of a potentially involved or threatened CRM. Other high-risk features present on MRI which can predict a poorer outcome include the presence of extramural venous invasion [16], extramural spread beyond 5 mm [17], increased nodal stage [18], and a low rectal tumor requiring abdominoperineal resection [19]. Recognition of these high-risk features enables appropriate treatment decisions regarding neoadjuvant therapy, with CRT generally reserved for high-risk patients with a potentially involved or threatened CRM on baseline imaging.

The use of neoadjuvant short-course radiotherapy (SCRT) or long-course chemoradiation (CRT) results in a reduction in local recurrence rates when compared to surgery alone [20•, 21•]. The degree of tumor downstaging following neoadjuvant CRT is variable and the rate of pathological complete response (pCR), defined as the complete absence of any residual cells within the resected surgical specimen, ranges from 0%–30% depending on the treatment regimen [21•, 22, 23]. Pathological complete response is a function of the stage of the primary tumor, the inherent sensitivity of the tumor to treatment, the dose of radiotherapy, the use of concomitant chemotherapy, the time interval between treatment and surgery, and the robustness of the pathological analysis performed. Several studies have suggested an association with pCR and outcome [24, 25] and the results of a pooled analysis demonstrated that pCR following neoadjuvant CRT in patients with rectal cancer is associated with improved disease-free and overall survival (OS) [26]. These data raise the possibility that in patients achieving a good response after neoadjuvant treatment, less invasive treatment options including local excision of the tumor or omission of surgery in the case of a clinical complete response could also be considered.

This article reviews the issues surrounding a non-surgical approach to the management of patients with locally advanced rectal cancer.

Current Treatment Options

The treatment for locally advanced rectal cancer involves a multimodality approach usually including radical surgery, radiotherapy, and chemotherapy. Treatment decisions regarding neoadjuvant treatment strategies are commonly made within a multidisciplinary team setting and rely on accurate tumor staging. Using high-resolution MRI, patients can be categorized into low, moderate, or high-risk based on the stage, the predicted relationship of the tumor to the CRM, lymph node status, degree of extramural spread, and presence of extramural venous invasion (Table 1).

Patients with low-risk disease are generally managed with surgery alone whereas those with moderate or high-risk disease should be considered for neoadjuvant treatment. There is variation worldwide in the management of patients with moderate-risk disease; the use of short-course radiation (SCRT), 25 Gy in 5 fractions followed by surgery a week later is common in Europe, whereas in the UK and USA there has been a move towards neoadjuvant long-course CRT. For those with high-risk disease long-course chemoradiation (45–50.4 Gy/28# with concurrent fluorouracil [5FU] or capecitabine) is widely accepted as a neoadjuvant treatment approach.

The use of SCRT is largely based on the results of the Swedish Rectal Cancer Trial which demonstrated a significant reduction in local recurrence and an OS benefit following SCRT and surgery compared to surgery alone. The 5-year local recurrence rate was 11% in the SCRT arm versus 27% in the surgery alone arm ($P<0.001$) and the 5-year OS was 58% versus 48% ($P=0.004$), respectively [20•]. The survival benefit was maintained at a median of 13 years follow-up and to date this remains the only neoadjuvant radiotherapy trial to demonstrate a survival benefit [27]. However, this trial was performed in the pre-TME era and following the introduction of TME surgery as standard of care, it was uncertain whether the low local recurrence rates following SCRT and TME were a result of the improved surgical technique or radiotherapy. The Dutch Colorectal Cancer Group subsequently assessed the role of SCRT with TME over TME alone. The trial demonstrated local recurrence rates of 2.4% in the surgery plus radiotherapy group versus 8.2% in the surgery alone group ($P<0.001$); there was no difference in OS. These results suggested that

Table 1 Prognostic classification of rectal cancer

Risk/histological feature	Low risk	Moderate risk	High risk
Extramural spread	≤5 mm	≥5 mm	≥5 mm
Nodal status	N0	N1–2	N2
CRM	Not at risk	Not at risk	At risk
Position of tumor	High	Low or high	Low
EMVI	Absent	Present	Present

CRM circumferential resection margin; *EMVI* extramural venous invasion; *N* node

the addition of SCRT remains beneficial in reducing local recurrence [28].

The benefit of concurrent chemotherapy with long-course radiotherapy was demonstrated in the EORTC 22921 study, a large randomized phase III trial. The trial demonstrated a significant reduction in local recurrence rates with the addition of 5FU to long-course radiotherapy regardless of whether the chemotherapy was administered preoperatively or postoperatively. Local recurrence rates at 5 years were 8.7%, 9.6%, and 7.6% in the groups that received chemotherapy preoperatively, postoperatively, or both, respectively, and 17.1% in the group that did not receive concurrent chemotherapy (P=0.002). There was no significant difference in OS between the groups (P=0.84) [29].

The CAO/ARO/AIO-94 German Rectal Study Group established that preoperative CRT is superior to postoperative CRT. Patients with locally advanced disease were randomized to receive preoperative or postoperative CRT with concurrent infusional 5FU. The local recurrence rates were reduced from 13% in the postoperative arm to 6% (P=0.006) in the preoperative arm. The benefit persisted after 11 years follow-up [30]. In addition, grade 3/4 toxicity was reduced in the preoperative arm (27% vs 40%, P=0.001) [21•]. The benefit of preoperative over postoperative radiotherapy was subsequently confirmed in a meta-analysis comparing outcomes of surgery for rectal cancer combined with preoperative or postoperative radiotherapy with those of surgery alone (Table 2) [31].

Deferral of Surgery

Tumor downstaging is not usually demonstrated after SCRT as tumor regression is integrally related to the time interval between treatment and surgery, and patients receiving SCRT usually proceed to surgery 7–10 days after completion of radiotherapy. Downstaging occurs following CRT; however, the optimal interval between completion of CRT and surgery is as yet unknown. Traditionally, surgery takes place 6–8 weeks after completion of CRT, but maximal tumor downstaging may require a longer period of time depending on individual tumor response.

In the Lyon 90–01 trial, patients with T2/3 mid-low rectal cancers were randomized to receive 39 Gy in 13 fractions with surgery following by a short interval (<2 weeks) or a long interval (6–8 weeks). A significantly better clinical tumor response (short interval 53.1% vs long interval 71%, P=0.007) and pathologic downstaging (short interval 10.3% vs long interval 26%) were demonstrated without a detrimental effect on morbidity, local relapse, or short-term survival [32]. Long-course chemoradiotherapy has subsequently superseded the hypofractionated regimen used in this study; however, these results suggest that a longer interval between

Table 2 Trials of neoadjuvant chemoradiation

Trial	No. of patients	Radiation dose	Arms	Chemotherapy	pCR (%)	Sphincter-sparing surgery	Local recurrence rate (5 year)	5-year OS	Grade 3/4 toxicity
CAO/ARO/AIO-94	823	50.4 Gy/28 #	Pre-op	CVI 5FU	8	39	6	76	27
Sauer et al. [21•]		50.4 Gy/28 # +5.4 Gy boost	Post-op	CVI 5FU		19	13	74	40
						P=0.004	P=0.006	P=0.80	P=0.001
FFCD-9203	733	45 Gy/25 #	Pre-op	CVI 5FU	11.4	58.3	8.1	67.9	14.9
Gerard et al. [89]		45 Gy/25 #	Pre-op	No chemo	3.6	57.7	16.5	67.4%	2.9
					P<0. 0001	P=0.837	P=0.004	P=0.684	
EORTC 22921	1011	45 Gy/25#	Pre-op RT	None	RT 5.3	RT 50.5	17.1	64.8	RT 7.4
Bosset et al. [29]			Pre-op RT + post-op chemo	Post-op bolus 5FU	CRT 13.7	CRT52.8	9.6	65.8	CRT 13.9
			Pre-op CRT	Bolus 5FU/LV	P<0.001	P=0.47	8.7	P=0.84	P<0.001
			Pre-op CRT + post-op chemo	Bolus 5FU/LV			7.6		
							P=0.002		
Polish Trial	316	25 Gy/5#	Short course	None	1	61	10.6*	67.2*	10.9
Bujko et al. [22]		50.4 Gy/28#	Chemoradiation	Bolus 5FU/LV	16	58	15.6*	66.2*	25
					P<0.001	P=0.57	P=0.210	NS	P<0.001

*4 year overall survival

preoperative radiotherapy and surgery is beneficial in terms of tumor downstaging.

There have been a number of retrospective reviews assessing the time interval between CRT and surgery. In one study patients with a time interval of greater than 7 weeks before surgery had higher rates of pCR and near pCR in addition to decreased local recurrence and improved DFS compared to those whose interval was less than 7 weeks [33]. The delay in time to surgery appears to have little impact on longer-term outcomes as reported in a review of 250 patients undergoing surgery within 12 weeks (48.4%) of completing CRT or greater than 12 weeks (51.6%). There were no statistical differences in OS (86% vs 81%) or disease-free survival (DFS) rates (56.5% and 58.9%) between patients according to the time interval [34]. This was, however, an underpowered non-randomized study; therefore, the results must be interpreted with caution.

A UK phase II study, one of the first prospective randomized trials in this setting, is currently evaluating the optimum interval between completion of radiotherapy and surgery. Patients are randomized to surgery at 6 or 12 weeks following completion of CRT irrespective of initial tumor stage on baseline MRI. This study plans to recruit 218 patients to determine whether greater downstaging is achieved after 12 weeks than 6 weeks after completion of neoadjuvant CRT.

In light of recent data suggesting an association between pCR and improved outcomes [26] and with up to 30% of patients achieving a pCR following neoadjuvant CRT, there is a growing argument for avoiding surgery in a selected group of patients. In a published series, 256 patients with resectable distal rectal cancer were treated with 5FU-based CRT and subsequently re-evaluated with a digital rectal examination, proctoscopy with repeat biopsies, CT of the pelvis, and a colonoscopy 8 weeks after completion of treatment. Seventy-one patients (26.8%) were deemed to have a complete clinical response and were observed under a strict follow-up program, 194 (73.2%) proceeded to radical surgery. Five-year overall and disease-free survival rates were 88% and 83% respectively in the resection group and 100% and 83% in the observation group [35]. Updated results after 360 patients had been treated demonstrated that local recurrence occurred in only five patients, all of whom were amenable to salvage surgery [36]. The long-term outcomes for patients with complete clinical response in this study were excellent and seem to suggest that a non-operative approach may be safe in a selected group of patients achieving complete clinical response following CRT.

These results have recently been replicated in a study of 21 patients who achieved a complete clinical response to CRT. Patients were followed up with MRI and endoscopy, and after a mean follow-up of 25 months only one patient had developed a local recurrence which was successfully salvaged with surgery [37].

The Deferral of Surgery trial, a UK phase II study, is currently recruiting patients to establish the time to maximum tumor response following CRT, and to investigate whether surgery can be safely avoided within the tight framework of the trial follow-up protocol, in a group of patients where the cancer becomes undetectable by imaging modalities after CRT. An update on the trial presented in 2011 reported that of the 22 patients recruited, 13 (59%) had maintained a complete response and 9 (41%) had developed tumor progression; of these, 7 were successfully salvaged with surgery while the other two declined surgery [38].

A concern with deferral of definitive treatment is the associated delay in commencing adjuvant chemotherapy and the subsequent risk of systemic relapse. Local recurrence rates following preoperative SCRT or CRT and surgery are low, however distant recurrence is reported in up to 30%–40% of cases. These patients should therefore still be considered adjuvant chemotherapy irrespective of the timing of their definitive local treatment.

In order to increase tumor downstaging and pCR rates a number of approaches have been evaluated including radiotherapy dose escalation, the use of more effective radiation sensitization, and the addition of neoadjuvant chemotherapy. In theory these approaches aim to increase the number of patients for whom a non-surgical approach could be appropriate.

Radiation Dose Escalation

Early dose escalation studies evaluating doses ≥50 Gy in rectal cancer demonstrate respectable pCR rates [39, 40]. In a matched pair analysis of 76 patients there was a suggestion of increased tumor downstaging in patients receiving 52.5 Gy in 30 fractions compared to standard CRT (45 Gy in 25 fractions). There was a trend toward increased grade I/II skin toxicity in the higher-dose group but no difference in grade III toxicity. The rate of pCR did not differ between the two groups (17.1% vs 15.8%, $P=0.83$) but T downstaging was greater with the higher dose (76.3% vs 51.3%, $P<0.001$) [41]. A study by Mohuiddin et al. of 5FU-based CRT with variable radiation doses demonstrated increased pCR rates in patients treated with radiation doses >55 Gy when compared to those with <50 Gy (44% vs 13%, $P=0.05$) [42].

Alternative methods of radiotherapy delivery to increase dose to the primary tumor while minimizing dose to the surrounding normal tissue include contact radiotherapy and endorectal brachytherapy. Contact radiotherapy was initially explored in early-stage tumors (T1/T2N0) by Papillon et al. [43] and more recently has been evaluated in combination with external beam radiotherapy (EBRT) allowing a boost to

be given to the primary tumor [44]. For more advanced tumors the use of endorectal high dose rate brachytherapy (HDR) allows a higher dose to be delivered to the primary tumor. Using a combined approach, doses of up to 100 Gy have been delivered without significantly affecting toxicity. In a study of 63 patients with T2/T3 N0/N1 disease treated with contact radiotherapy, EBRT, and interstitial brachytherapy there was no acute grade 3 or 4 toxicity although late rectal bleeding occurred in 38% of patients. The 5-year survival rate was 84% (T2) and 53% (T3) and local control rate was 63% [45].

In a feasibility study of endorectal HDR, 50 patients with T3 disease were treated with EBRT 60 Gy/30 fractions with concurrent uracil and tegafur with a 5 Gy single fraction endorectal boost to the tumor bed. Forty-eight patients underwent surgery and high rates of tumor regression were demonstrated with low rates of toxicity [46]. These results led to a randomized phase III study of 50.4 Gy/28# with concomitant uftoral and leucovorin with or without an HDR endorectal boost (10 Gy in two 5 Gy fractions). No difference in pCR was demonstrated; however, the R0 resection rate was significantly increased following the endorectal boost (90% vs 99%, P=0.03). There was no significant increase in toxicity or surgical complications [47].

More recently, intensity-modulated radiotherapy (IMRT) using multiple radiation fields to create highly conformal dose distributions has been evaluated in an attempt to minimize the doses to adjacent critical pelvic structures for patients with locally advanced rectal cancer. In a dose-planning study radiotherapy was planned for each patient using 3D conformal radiotherapy and 7 field IMRT. IMRT planning improved target conformity and decreased irradiation of the organs at risk but at the expense of increased target heterogeneity [48]. These results have been replicated in small clinical studies [49] and in a retrospective review of patients treated with IMRT but have yet to be confirmed in larger studies [50]. IMRT with concurrent capecitabine and oxaliplatin was demonstrated to be feasible in the phase II RTOG 0822 study [51].

In addition to dose escalation and alternative methods of radiotherapy delivery, various imaging modalities to improve radiotherapy planning are under evaluation including the use of FDG-PET scans to increase dose to PET-positive regions only [52].

Radiosensitization

Intensification of chemoradiation with the addition of oxaliplatin to 5FU or capecitabine-based chemoradiotherapy demonstrated improved pCR rates in phase II trials [53–56]; however, these results have not been replicated in phase III studies. The ACCORD 12/0405/Prodige 2 [57], STAR [58], and NSABP R-04 phase III trials [59] failed to demonstrate benefit with the addition of oxaliplatin to CRT and all reported increased rates of grade 3/4 toxicity. The CAOI/ARO/AIO-04 trial demonstrated an improvement in pCR (12.8% vs 16.5%, P=0.045) with no increase in toxicity; however, this was an unplanned exploratory analysis [60]. The PETTAC-6 trial of concurrent capecitabine-based CRT with or without oxaliplatin has completed accrual and the results are awaited. Although the long-term outcomes of these trials have not yet been reported it seems apparent with over 3000 patients in these randomized phase III trials that oxaliplatin does not confer any additional benefit in radiosensitization in the clinical setting when compared to fluorouracil-based CRT. Whether this is secondary to the increased rates of toxicity demonstrated with oxaliplatin or that oxaliplatin is simply not an effective radiosensitizer in rectal cancer remains unclear.

The results of phase II trials demonstrate irinotecan-based CRT is well tolerated and results in pCR rates between 15%–28% [23, 61–64], although there is concern over rates of surgical complications with irinotecan-based regimens. The addition of irinotecan resulted in increased grade 3/4 diarrhea in these studies (range 4%–45%) [23, 61, 63, 65, 66]. A randomized phase III trial of concurrent irinotecan and capecitabine versus capecitabine-based CRT is ongoing (ARISTOTLE); the primary endpoint of this study is DFS and the study plans to recruit 920 patients.

The addition of targeted agents to CRT has been assessed in several phase II studies [67–74] and a recent pooled analysis of CRT studies with the addition of the anti-EGFR monoclonal antibody cetuximab demonstrated a pCR rate of 9% (range 0%–20%), with manageable toxicity [75]. Bevacizumab has been incorporated into neoadjuvant CRT with variable toxicity and pCR rates (0%–32%) [76]. The data on bevacizumab is limited by the relatively small numbers of patients in these studies; therefore at present conclusion regarding the benefit of the addition of bevacizumab cannot be made. In addition, although the acute complication rate appears to be similar, a number of patients developed wound complications requiring surgical intervention and the impact of bevacizumab on perineal wound and anastomotic healing requires further study.

Neoadjuvant Chemotherapy

The rationale for neoadjuvant chemotherapy includes early initiation of systemic chemotherapy, increased compliance rates when compared to adjuvant chemotherapy delivery, early identification of patients with aggressive biology who do not benefit from standard regimens, and may require intensification of treatment and downstaging of the primary tumor. Theoretically, increased tumor downstaging prior to CRT may increase the number of patients in whom a non-surgical approach could be employed.

Phase II trials evaluating the addition of neoadjuvant chemotherapy to the treatment paradigm of locally advanced rectal cancer have demonstrated high radiological response rates and encouraging longer-term outcomes. A single arm phase II trial (EXPERT) evaluated neoadjuvant oxaliplatin plus capecitabine (CAPOX) followed by capecitabine-based CRT and TME in 105 patients with MRI-defined poor prognosis rectal cancer. Radiological response rates were 74% following neoadjuvant chemotherapy and 89% after CRT with a pCR of 20%. The 5-year PFS and OS were 64% and 75% respectively despite the poor risk population [77]. The subsequent phase II European multicenter trial (EXPERT-C) evaluated addition of cetuximab to a similar treatment protocol. In the *KRAS/BRAF* wild-type population addition of cetuximab resulted in a 20% improvement in radiological response to neoadjuvant chemotherapy (CAPOX+C 71% vs CAPOX 51%, P=0.038) and this significant improvement was maintained after CRT (CAPOX +C 93% vs CAPOX 75%, P=0.028). There was a significant overall survival benefit in the wild-type patients receiving cetuximab (CAPOX + C 96% vs CAPOX 81%, HR 0.27, 95% CI 0.07–0.99, P=0.035) [78].

In a single arm phase II trial of neoadjuvant chemotherapy, selected patients with stage II or III disease (excluding T4 or bulky disease) received six cycles of FOLFOX/bevacizumab. Patients with a partial or complete response went straight to surgery, with selective post-op CRT given to those with a positive histological CRM; patients with stable or progressive disease after the chemotherapy had CRT prior to surgery. Early results presented at GI ASCO 2011 demonstrated that 30/32 patients responded to treatment and did not require CRT. The chemotherapy was well tolerated resulting in a pCR rate of 25%; however, longer-term follow-up is required to assess the impact on local control, PFS, and OS in these patients. Theoretically, a similar approach, omitting surgery could be evaluated with patients achieving a complete response after neoadjuvant chemotherapy and CRT. Accurate assessment of post-treatment imaging and prediction of response to preoperative treatment would potentially allow patient selection for non-surgical management and further clinical trials are required to explore this option.

Patient Selection

The challenge for non-operative approaches is patient selection and the availability of suitable tools to predict response to treatment and appropriately interpret post-treatment imaging in order to identify those with a clinical or pathological complete response. Improvements in imaging techniques, particularly the use of high-resolution MRI, have increased the ability to predict a potentially involved or threatened CRM prior to TME. The specificity of MRI in predicting a clear CRM was 92% in a study of 408 patients who underwent MRI pre-TME [79•]. More recent data suggest that MRI tumor regression grade (mrTRG) based on the degree of low signal intensity appearances of fibrosis,

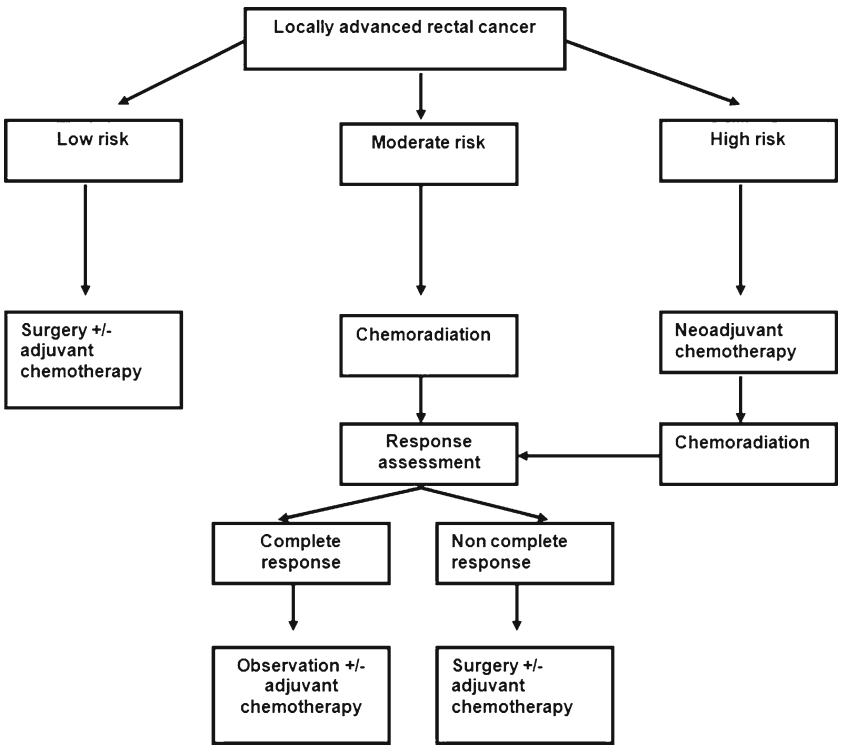

Fig. 1 Potential treatment paradigm for non-surgical approach

can predict for improved outcomes following CRT in rectal cancer patients. Five-year survival for patients with poor mrTRG was 27% compared to 72% for those with good mrTRG (P=0.001) and DFS was 31% versus 64% (P=0.007) respectively. However, this has yet to be prospectively validated [80].

Alterative prediction tools include the use of PET and molecular biomarkers. While the use of ^{18}FDG-PET in post-treatment response assessment is well established in a number of solid tumors, most notably Hodgkin's and non-Hodgkin's lymphoma, its role in post-treatment assessment of rectal cancer is less well established. A number of studies have demonstrated an association between a decrease in standardized uptake value and pathological response [81, 82] and two small studies have suggested a prognostic role with post-treatment PET predicting unfavorable tumor biology and worse prognosis [83, 84].

Although a number of molecular biomarkers for response to neoadjuvant chemoradiation for rectal cancer have been investigated, none have yet been incorporated into routine clinical practice. A literature review of commonly researched biomarkers evaluated the six most common putative markers, p53, EGFR, thymidylate synthase (TYMS), Ki-67, p21, and bcl-2/bax. Unfortunately, the majority of these studies were retrospective with relatively small numbers of patients. In addition, significant variation in the CRT scheduling and methodology used to evaluate the biomarkers complicate interpretation. The review concluded that TYMS, EGFR polymorphisms, and p21 demonstrated potential to predict response to treatment but nevertheless require further evaluation [85]. Interestingly, direct sequencing of p53 has demonstrated that p53 gene mutations rather than levels of expression may be associated with radio resistance [86].

Molecular markers for response to chemotherapy in colorectal cancer have also been evaluated with particular focus on the pathways involved, agents targeting the epidermal growth factor, and angiogenesis pathways. The only biomarker to date to be routinely incorporated into clinical practice is *KRAS* status; the presence of a *KRAS* mutation predicts for lack of response to anti-EGFR monoclonal antibodies [87]. However, a significant proportion of patients with *KRAS* wild-type tumors (60%) do not respond to cetuximab, suggesting the presence of mutations/aberrations in the downstream effectors of the EGFR pathway. The downstream effectors *BRAF, NRAS,* and *PI3KCA* mutations have been associated with a lack of response and the so-called "quadruple negatives" (*KRAS, BRAF, NRAS,* and *PI3KCA* wild-type tumors) demonstrate improved response rates [88]. Despite extensive international research in the field of angiogenesis, the downstream signaling cascade which follows VEGF receptor activation remains poorly understood and to date, no biomarker has demonstrated a predictive impact on anti-angiogenic treatment outcome. Clearly much work is still needed to identify reliable biomarkers that can be incorporated into clinical practice and whether the potential biomarkers for radiosensitivity are robust enough to be incorporated into clinical trials remains unclear.

Conclusions

The standard of care for locally advanced rectal cancer remains a multimodality approach with radiotherapy, chemotherapy, and surgery. Neoadjuvant short-course radiotherapy and long-course chemoradiation reduce local recurrence rates when compared to surgery alone, with CRT generally offered to higher risk patients with a potentially involved or threatened CRM on baseline imaging.

There is evidence to suggest that a longer time interval between completion of CRT and surgery appears to increase tumor downstaging; in addition, recent data indicate that a pCR following CRT is associated with improved outcomes. Together these data imply that a non-surgical approach may be appropriate in a highly selected group of patients achieving a complete response to neoadjuvant treatment (Fig. 1). Intensification of chemoradiation schedules has, to date, failed to significantly impact on pCR rates; whether this is related to suboptimal dosing secondary to increased toxicity with additional agents or whether fluorouracil-based CRT provides optimal radiosensitization is still unclear. Radiation dose escalation techniques appear to increase tumor downstaging and warrant further investigation. The introduction of neoadjuvant chemotherapy prior to CRT in phase II studies results in high rates of radiological tumor regression and may aid the shift in the treatment paradigm toward the non-surgical approach. Undoubtedly these approaches require prospective evaluation within a clinical trial setting incorporating modern imaging techniques, and tissue biomarkers to allow accurate prediction and assessment of response.

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