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RADIATION THERAPY AND RADIATION THERAPY INNOVATIONS IN COLORECTAL CANCER (JY WO, SECTION EDITOR)

Optimal Sequencing of Neoadjuvant Therapies (NAT) in Rectal Cancer: Upfront Chemotherapy vs. Upfront Chemoradiation

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Abstract New strategies for the treatment of cancer in the rectum should be directed towards the improvement of micrometastatic disease and the reduction of long-term sequelae, without prejudice to good local control. To achieve this, in the last decade, new strategies have been postulated. Treatment with preoperative chemotherapy (CT) alone or induction CT followed by chemoradiation CRT/short course radiation (CRT/SCPRT) or CRT/SCPRT and consolidative CT is being planned. We currently have data from phase II studies with results of stimulating efficacy and/or compliance. New single-arm and randomized trial is underway and will allow us to know the impact on survival outcomes and long-term sequelae of these strategies.

Keywords Consolidation chemotherapy · Chemoradiation · Induction chemotherapy · Rectal cancer · Total Neoadjuvant therapy

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Introduction

Prior to the current surgical operation of total mesorectal excision (TME), surgeons employed blunt dissection techniques with the fingers. High rates of local pelvic recurrence were reported, which caused devastating symptoms and were difficult to palliate. Also, 30–50% required a permanent stoma. Hence, avoidance of LR and the possibility of sphincter sparing have long dominated decision-making.

Postoperative trials during the 1980s showed a significant benefit for adjuvant concurrent chemoradiation (CRT) in terms of local recurrence (LR), disease-free survival (DFS) and overall survival (OS) [1, 2], which has now been extrapolated to the preoperative setting. Preoperative CRT was then compared to postoperative CRT in the German Trial CAO/ARO/AIO—94 [3]. Acute and late toxicity was significantly less with the preoperative approach. Loco-regional failure was significantly lower at 7% in the preoperative arm vs. 10% in the postoperative arm. There was, however, no difference in the distant metastases rate or OS [4]. Further trials investigating preoperative CRT all showed a reduction in LR [5, 6], but did not impact on OS. For more advanced unresectable cases, the addition of fluoropyrimidines to radiation has favourable effects on response and relapse-free survival compared to RT alone, with a trend to improved OS [7]

In Europe, randomized trials [8–11] examined short course preoperative radiotherapy (SCPRT), accelerated and hypofractionated radiotherapy, administering 25 Gy in five fractions over 5 days. SCPRT also reduced LR rates and established SCPRT as a standard component of treatment for rectal cancer.

Thus, there are now three distinct current options which can deliver radiotherapy locally to tumour in the pelvis to reduce LR. SCPRT and long-course preoperative CRT are both considered standard neoadjuvant strategies. The

integration of chemotherapy (CT) is attractive as a radiosensitizing agent within the radiation field in the pelvis and may have systemic effects.

In addition, high dose rate endoluminal brachytherapy (HDR-BRT) offers a third preoperative alternative. A pCR rate of 27% and an actuarial LR rate of only 4.8% were reported after HDR-BRT [12].

A matched analysis compared SCPRT and HDR-BRT in terms of LR and OS between Dutch and Canadian centres [13] and demonstrated no significant differences. SCPRT and immediate surgery have also been compared directly to long-course CRT in randomized studies. CRT and SCPRT appear equivalent in terms of LR, DFS and overall survival (OS) [14–16]. More recently, the Polish Rectal study showed more adverse events associated with CRT compared with SCPRT followed by consolidative FOLFOX for 3 cycles, but no statistically significant differences in postoperative complications [17••].

CRT leads to downstaging/downsizing, and 10–20% of patients achieve a pathological complete response (pCR). Hence, many believe this excellent response facilitates sphincter-preserving surgery (SPS). The results of the German trial indirectly support this view [3], but specifically designed trials [18•] and meta-analyses have failed to confirm CRT increases the chance of SPS. However, efforts are continuing to intensify multimodality treatments both to increase SPS and for organ preservation with avoidance of the need for surgery. CRT has been considered the treatment of choice to maximize downstaging in locally advanced, fixed or unresectable tumours, although SCPRT followed by systemic CT with oxaliplatin may provide similar results with less acute toxicity [18•].

Currently, with the standard of good quality TME, LR has become a rare event in patients with stage I, II and III rectal cancer. However, outcomes with the standard treatment strategies are still far from optimal. There are significant long-term sequelae related to surgery and radiotherapy, There is considerable overtreatment relating to inaccurate staging techniques. A substantial risk of distant relapse also highlights the ineffectiveness of the subsystemic fluoropyrimidine component of chemoradiotherapy against micrometastatic disease. All of which dictate a pressing need for improvement.

Patients treated with SCPRT prior to TME have less potential for LR compared to patients undergoing TME alone, but this benefit is mainly limited to subgroups (i.e. stage III), underscoring the need for accurate preoperative staging [19].

In the case of patients treated with preoperative CRT or SCPRT, adjuvant CT has shown no benefit compared to observation in any of the four phase III studies performed to date [20–23]. Poor adherence to systemic therapy in some studies [20–22], inclusion of low-risk patients due to the use of old methods of staging, lack of statistical power by early closure of the study [21, 23] as well as the use of suboptimal systemic treatments [20, 22, 23] are among the causes of negative outcomes. More recently, modern studies with adjuvant CT regimens with FOLFOX have shown benefit compared with FU/LV in patients previously treated with CRT and surgery [24, 25].

Based on these observations, a new generation of clinical trials in stages II and III rectal cancer that mandate MRI as a staging technique include more effective CT regimens and utilize novel strategies that allow an optimal sequence of treatment modalities are being carried out in recent years.

In this article, we review the arguments that justify these new treatment strategies, current data, as well as ongoing efforts to further evaluate the impact of this approach

Preoperative CT Without Radiation

SCPRT and CRT have improved local control, but both treatment strategies are associated with an increased incidence of serious side effects, with approximately 5–10% of patients experiencing grade 3–4 late morbidity [10, 15, 16, 26]. The concept of locally advanced rectal cancer (LARC) encompasses the group of middle and distal third rectal tumours (i.e. with the lower border of the tumour ≤12 cm from the anal verge) with a heterogeneous prognosis. Patients with rectal cancer in the middle third and T3 tumours with no predicted involvement of the mesorectal fascia (MRF) represent an intermediate risk group in which the risk of distant relapse predominates over the risk of LR. In a recent MERCURY study, 122 patients with MRI-predicted safe circumferential resection margins (CRM), regardless of MRI N stage, were included. Patients were treated with good quality TME surgery alone. The population included 57 cStage II tumours and 66 patients with good prognosis cStage III tumours (i.e. mrT2, T3a and T3b and mrN+). In this later group, 4 patients (6%) had a pathological involved CRM. Overall, the LR and distant relapses rates were 3 and 20%, respectively [27]. In addition, retrospective series of metastatic colorectal cancer patients with intact primary tumours have shown significant primary tumour regression with pCR following modern systemic CT [28]

These observations suggest that induction with CT in this group of patients (i.e. T3 with clear MRF) is an attractive strategy, producing the local benefits of preoperative treatment and allowing early treatment of micrometastases at therapeutic doses without the long-term side effects of radiation.

Selected Published Series

Results of two single-arm trials in T3, middle third rectal tumours with clear MRF have been reported. Both trials used a similar treatment strategy with 12 weeks of induction with bevacizumab and systematic CT treatment, while CRT was

only given for poor response. The MSKCC pilot trial included 32 patients with locally advanced rectal cancer, who were candidates low anterior resection and cT2-3 N+ and cT3 any N (with ERUS and MRI). Induction CT consisted of 4 cycles neoadjuvant of FOLFOX + Bevacizumab and 2 subsequent cycles FOLFOX alone. Patients with stable/progressive disease went on to receive CRT; however, responders proceeding straight to TME. Postoperative CRT was considered for close/positive margins. Postoperative FOLFOX × 6 was recommended, but adjuvant regiments were left to the clinician discretion. pCR and R0 resection rates were 25 and 100%, respectively. With a median follow-up of 54 months, local and distant relapse were 0 and 12.5%, respectively, and 4-year DSF was 92%. Only two participants, both intolerant of FOLFOX/bevacizumab, received preoperative CRT [29••].

The Grupo Español Multidisciplinar Cancer Digestivo (GEMCAD) 0801 multicentric, phase II trial recruited 46 patients with T3, middle third and MRF clear rectal cancer selected by MRI. Patients receive 4 cycles of CAPOX-bevacizumab (last cycle without Bev), and preoperative CRT was recommended only in cases of evidence of progression. The overall response rate was 78%, R0 100%, pCR 20% and downstaging 48% [30•]. An unexpectedly high rate (15%) of anastomotic leakage (AL) and two deaths were probably related to the use of bevacizumab during the treatment period. No patient received preoperative CRT. In a second report from the same trial with a median follow-up of 41 months, LR only and distant relapse were 6 and 21%, respectively, and DFS was 61%. Baseline MRI assessment of extramural venous invasion (EMVI) status has been identified as the most important clinical risk factor related with DFS and recurrence. Three-year DFS for mrEMVI-positive patients was 44 vs. 96% for mrEMVI-negative patients ($p = 0.0001$), and 3-year cumulative incidence of recurrence for mrEMVI-positive patients was 44 vs. 4% for mrEMVI-negative patients ($p = 0.0019$). The authors conclude these patients should benefit from intensive preoperative CT [31]

In addition, two Japanese studies used a scheme identical to that of GEMCAD 0801, but in a high-risk population of middle or distal third cancers. Patients underwent surgery and CRT was not offered. Uehara et al. recruited 32 patients, of which 60% were cT4. The pCR was 13%, and the anastomotic leakage rate was 28% with 3% mortality [32]. Hasegawa et al. recruited 25 high-risk patients (T4 in 75%) and achieved a pCR rate of 4% [33]. A third trial from Japan with 8 weeks induction CT (2 cycles of Irinotecan, Fluorouracil, Leucovorin (IFL)) in T3, T4 middle or low rectal cancer also reported a 4% pCR [34].

Primary results from a three-arm randomized phase III trial has been recently reported [35•] comparing neoadjuvant fluorouracil/leucovorin (5FU/LV) combined with RT followed by adjuvant 5FU/LV (arm A) with neoadjuvant mFOLFOX6 combined with RT and adjuvant mFOLFOX6 (arm B) with the same regimen without RT (arm C). A total of 165 patients were randomized to each group. Patients with rectal cStage II or III were included. No stratification was made, and T4 patients were 34.6% in arm A, 34% in arm B and 30.3% in group C. The rates of pCR were 14, 27.5 and 6.6% in each group. Patients in arm C without RT achieved less pCR rates but a lower rate of postoperative surgical complications. Three-year DFS (primary endpoint) will be available during 2017.

In summary, systemic treatment in T3 tumours results in promising activity, high R0 resection and low LR rates, which justify new studies in this population with this strategy. However, the considerable surgical morbidity with the addition of bevacizumab to fluoropyrimidine/oxaliplatin CT does not support further investigation of this specific regimen. Pathologic CR seem to be related to tumour size, as evidenced by the lower rate observed in the other studies analyzed that included T4 tumours.

Ongoing Trials

The Preoperative Radiation or Selective Preoperative Radiation and Evaluation Before Chemotherapy and TME study (NCT01515787) is a phase II/III randomized trial. Patients who are candidates for sphincter preservation at presentation and with cT2N1, cT3N0 or T3N1 are randomized to standard CRT followed by TME vs. neoadjuvant FOLFOX followed by objective response determination. Responding patients proceed directly to surgery. The primary endpoint is complete resection rates (phase II portion) and disease-free survival/time to LR (phase III portion). This trial could establish whether selective omission of radiotherapy to patients deriving clinical benefit from systemic neoadjuvant CT provides adequate oncologic outcomes with less toxicity.

A British trial investigated the addition of bevacizumab to combination chemotherapy in rectal cancer until surgery trial (NCT01650428). In this multi-centre randomized phase II study, patients with T3, MRF clear tumours in the middle third were randomized to 12 weeks of neoadjuvant systemic therapy with either FOLFOX with bevacizumab or FOLFOXIRI (5FU, leucovorin, oxaliplatin and irinotecan) with bevacizumab. This trial stopped early because of lack of recruitment, and results are not yet reported.

In this intermediate risk population, the GEMCAD is now performing a phase II trial exploring the value of incorporating anti-epidermal growth factor receptor therapies to the appropriately extended BRAF, PIK3CA, RAS wild-type population neoadjuvant setting (NCT03000374).

As other new therapies become clinically relevant in the metastatic disease setting, the opportunity to bring them into the neoadjuvant rectal cancer treatment paradigm represents a new era in rectal cancer personalized patient management and clinical trial design.

Upfront Chemotherapy Followed by CRT (SCPRT) and TME

A more effective systemic treatment against micrometastatic disease should be a priority in the new generation of clinical trials in LARC. Current figures for distant disease in stages II and III overall are 30% and are still significantly higher in some subgroups of patients with poor prognostic features (i.e. T4, N2 or EMVI-positive tumours) [30•, 36, 37]

Upfront CT offers some theoretical advantages, such as the early treatment of micrometastases, with optimal exposure to systemic CT, rapid relief of local symptoms and a shorter time to cope with a stoma. This strategy, however, may also be associated with its own caveats, such as selection of radioresistant clones, induction of accelerated repopulation [38] and overtreatment if we are not able to detect high-risk patients accurately. However, although currently a reliable assessment of the pretherapeutic mesorectal regional lymph node status is not possible by the present imaging modalities, thin-slice high-resolution MRI can identify accurately the extent of extramural tumour spread, the EMVI and the status of MRF [36, 39]

Evidence from Selected Series

The British Expert trial showed that intensification of systemic therapy with neoadjuvant combination oxaliplatin-based CT before CRT and surgery was feasible in high-risk potentially operable rectal cancer, with acceptable safety and promising outcomes [40•].

Based on these encouraging results, the Spanish GCR-3 completed a randomized phase II trial in a high-risk population selected by MRI, comparing this approach with conventional preoperative CRT followed by surgery and postoperative adjuvant CT. Primary results were reported in 2010 [41••]. Compared with postoperative adjuvant capecitabine-oxaliplatin (CAPOX), induction CAPOX before CRT had similar pCR and complete resection rates while at the same time achieving a significant more favourable compliance (51 vs. 92% in the adjuvant vs. induction group ($p = 0.0001$) and toxicity profiles (g3/4 toxicities 51% during adjuvant vs. 19% during induction ($p = 0.0004$) [41••]. Updated results of this trial showed that delay from diagnosis to surgery due to the induction CT had no negative impact in 5-year LR (2.1 and 2% in the R0 + R1 population in the adjuvant vs. induction arm) 5-y DFS Five-year DFS in both arms (64% in adjuvant vs. 62% induction arm) [42].

Two randomized phase II trials [43, 44] and several single-arm studies [45–48] have been published since 2010. The randomized phase II EXPERT-C study evaluated, in high-risk patients selected by MRI, the addition of cetuximab to neoadjuvant CT before CRT [43]. As compared with induction CAPOX, the addition of cetuximab to neoadjuvant CT did not improve either pCR or 5-year PFS and OS, although a significant increase in radiological response rate was observed. In a biomarker subanalysis, TP53 wild-type patients ($n = 69$) who received cetuximab had a statistically significant better PFS (89.3 vs. 65.0%; $p = 0.02$) and 5-year OS (92.7 vs. 67.5%; $p = 0.02$) [49].

Marechal et al. compared preoperative CRT vs. induction FOLFOX followed by CRT. Adjuvant CT was at the discretion of the treating physician. pCR rate was similar, but higher overall toxicity was associated to the induction group [44].

Single-arm series included patients with middle and distal third cancers, clinical stage T3-T4/N+, except series from Perez et al. that also included some patients with clinical stage T1-T2/N+. Three used CAPOX, 2 or 4 cycles before CRT, and two used FOLFOX as the induction regimen. Compliance was high for both induction CT (85–92%) and CRT (83–100%). pCR rates varied between 20 and 36%. Notably, the higher pCR was seen in the trial that combined bevacizumab with induction CT and with CRT, but in this trial, 24% of patients required reoperation. High 4% mortality rate occurred in the series using CAPOX as induction CT.

The UK COPERNICUS multicentre phase II study evaluated the strategy of induction CT prior to SCPRT (instead of CRT) with 8 weeks of FOLFOX-like induction CT before SCPRT, then immediate surgery. Of 60 enrolled patients (88% cStage III), 57 underwent surgical resection with 100% complete resections (R0 surgical resections) and a 12% pCR [50]. The main aspects of these phase II trials are summarized in Table 1.

Ongoing Trials with Induction CT Followed by CRT

Efforts to augment the standard backbone of cytotoxic CT (fluoropyrimidine and oxaliplatin) with novel therapeutics are well under way.

The Spanish GEMCAD group is testing the inclusion of anti-vascular endothelial growth factor (VEGF) therapy with neoadjuvant FOLFOX (5FU, leucovorin and oxaliplatin). The induction FOLFOX with or without aflibercept followed by chemoRT in high risk locally advanced rectal cancer (RIA Trial) (NCT02340949; GEMCAD-1402) is a randomized phase II multi-centre study. The primary hypothesis is that the administration of aflibercept and CT prior to chemoRT and surgery can improve efficacy (via normalization of the tumour vasculature) without compromising safety (by moving surgery further away from VEGF administration). Primary endpoint is pCR.

Two French randomized trials are ongoing: Prodige23 is a phase III comparing preoperative CRT vs. induction CT with 6 cycles of FOLFIRINOX followed by CRT and surgery for patients with resectable high-risk LAR cancer with 3-year DFS as the primary endpoint (NCT01804790). The GRECCAR 12 compares 4 cycles of FOLFIRINOX followed

Table 1 Phase II randomized trials of induction chemotherapy followed by chemoradiotherapy (CRT) and surgery in LARC patients

	Number	Selection	Treatment	Outcomes	Toxicity	Compliance
GCR3 Fernández-Martos [24, 25]	108	MRI +/- EUS Middle third cT3/CRM+/cT3N+/cT4 resectable Lower third any T3	Arm A: CRT: CAPOX + 50.4 Gy Surgery: 6 weeks after CRT Adjuvant CT: CAPOX 4 cycles Arm B: Induction CT: CAPOX 4 cycles CRT: Same as arm A Surgery: Same as arm A	Arm A vs. Arm B • pCR 13 vs. 14% ($p = 0.94$) • Downstaging 58 vs. 43% ($p = 0.13$) • R0 resections 87 vs .86% ($p = 0.40$) • 5-year DFS 64 vs. 62% ($p = 0.85$) • 5-year LR rate 2 vs. 5% ($p = 0.61$) • 5-year DM rate 21 vs. 23% ($p = 0.79$)	Grade 3–4 during CT/RT 29 vs. 23% ($p = 0.360$) Grade 3–4 during adjuvant/induction 54 vs. 19% ($p = 0.0004$) 3 deaths in Arm A 1 mesenteric thrombosis 1 myocardial infarction 1 suicide 3 deaths in Arm B 2 anastomotic leak 1 major depression	RT compliance Arm A: 80% Arm B: 85% Adjuvant CT (arm A) 76% started CT 57% completed treatment Induction CT (arm B) 100% started CT 94% completed treatment Arm A vs. Arm B ($p < 0.0001$)
Marechal [28]	57	MRI and EUS T2-T4/N+	Arm A: CRT: 5FU + 45 Gy Surgery: 6–8 weeks after CRT Arm B: Induction CT: FOLFOX6 2 cycles CRT: Same as Arm A Surgery: Same as Arm AAdjuvant CT: investigator's discretion	Arm A vs. Arm B • pCR 28 vs. 25% ($p = 0.92$) • ypT0-1N0: 34 vs. 32% ($p = 0.85$) • T downstaging: 48 vs. 46% ($p = 0.99$) • N downstaging: 55 vs. 43% ($p = 0.64$)	Grade 3–4 during CRT/induction 7 vs 36% ($p = 0.017$) 1 death in Arm B 1 febrile neutropenia	Complete CRT 100% in arm A 96% in arm B Complete induction: 96%
EXPERT-C Dewdney [26, 27]	165	MRI cT3 below elevators, T4, EMVI+ or CRM+	Arm A: Induction CT: CAPOX 4 cycles CRT: Capecitabine + 50.4 Gy Surgery: 4–6 weeks after CRT Adjuvant CT: CAPOX 4 cycles Arm B: Induction CT: CAPOX + cetuximab 4 cycles CRT: capecitabine + cetuximab + 50.4 GySurgery: same as Arm A Adjuvant CT: CAPOX + cetuximab 4 cycles	Arm A vs. Arm B Radiological response rate: 54 vs. 64% ($p = 0.041$) • Radiological response rate in wild-type patients 51 vs. 71% ($p = 0.038$) • R0 resections 92 vs. 96% In TP53 wild-type patients • PFS: 65 vs. 89.3% $p = 0.02$ • 5-year OS: 67.5 vs. 92.7% $p = 0.02$	Grade 3–4 during induction 81 vs. 83% Grade 3–4 during CRT 75 vs. 78% Grade 3–4 during adjuvant CT 52 vs. 65% 3 deaths in Arm A 1 during induction 2 surgery complications 1 death in Arm B 1 during induction	Complete induction CT 91 vs. 93% Complete CRT 91 vs. 90% Complete adjuvant CT 62 vs. 72%

MRI magnetic resonance image, *CRM* circumferential resection margin, *CT* chemotherapy, *CRT* chemoradiotherapy, *pCR* pathological complete response, *LR* local recurrence, *DM* distant metastases, *OS* overall survival, *DFS* disease-free survival, *EMVI* extramural vascular invasion

by CRT vs. standard CRT. All patients would then proceed to undergo either conventional surgery or local excision depending on response. Patients must have cT2 or cT3 tumours, and the primary study end point is rate of organ preservation and absence of stoma at 1 year (NCT02514278)

Upfront Chemoradiation/Radiation

Given the three radiotherapy options described above (CRT, SCPRT and HD-BRT), investigators have explored a number of different strategies to intensify neoadjuvant treatment to increase the rate of complete clinical response and pCR and improve long-term oncological outcomes. Histopathological evidence after CRT suggests about a third of patients have tumours that are resistant and not down-staged by CRT [51, 52].

These intensification strategies include escalation of the radiotherapy component or adding CT before, concurrently or after the radiotherapy/CRT. The intensity of SCPRT does not easily allow integration of concurrent preoperative CT, although it could be argued that standard fluoropyrimidine-based CRT does not utilize fully systemic doses of CT. Most intensification strategies have focused on a CRT platform, but SCPRT also allows some integration of induction [50], concurrent [53] and consolidation CT [54, 55] prior to, during and following SCPRT, respectively.

Intensification of Radiotherapy

NCCN guidelines recommend preoperative CRT (45–50 Gy in 25–28 fractions, with an optional boost of 5.4 Gy in 3 fractions), SCPRT and/or neoadjuvant CT in a total neoadjuvant approach. The overall duration inclusive of CT and radiation therapy should not exceed 6 months (NCCN guidelines 2016) [56]. This represents a relatively modest total dose (45–50.4 Gy).

A phase III randomized trial comparing a novel arm, where both oxaliplatin was added and radiotherapy escalated to 50 Gy against a control arm using capecitabine and 45 Gy, increased the pCR rate and concluded that 50 Gy is a new standard [57].

The efficacy could be enhanced by dose escalation of the radiotherapy with additional fractions of external beam radiotherapy by adding an HD-BRT boost or by shortening the overall treatment time. These strategies can be achieved by intensity-modulated radiotherapy (IMRT) using a simultaneous integrated boost [58] because of the increased precision of IMRT and image-guided radiotherapy [59].

Studies imply a significant dose-response relationship for radiotherapy within preoperative CRT regimens [60, 61]. The former derived a theoretical model suggesting that to achieve a pCR in 50% of cases requires a dose escalation to at least 90 Gy to primary tumour [60]. However, such doses cannot be delivered safely via external beam treatments and require an HD-BRT boost, but it is harder to escalate nodal doses in the pelvis safely. When a randomized trial explored the escalation of RT dose within CRT with a HD-BRT boost, there was no increase in the pCR rate [62]. The number of R0 resection rates increased, but long-term outcomes did not improve. A prospective study in small early cancers dose-escalated radiotherapy within CRT (60 Gy in 30 fractions to primary tumour, 50 Gy in 30 fractions to elective lymph node volumes) with a 5-Gy HD-BRT boost [63]. Preliminary results showed 40 patients achieved a clinical CR, and local recurrence at 1 year was only 15·5% with acceptable sphincter function.

Intensification of CRT

In rectal cancer, more sophisticated computer technology, imaging and radiation delivery have been matched by the development of an increasing array of biological agents. However, improvements in concurrent chemoradiotherapy have not kept pace, and fluoropyrimidines remain the mainstay of concurrent chemoradiation regimens. Other cytotoxic and biological agents have been investigated as partners of 5FU-based chemoradiation, but without consistent success.

Fluoropyrimidine-Based Chemoradiation

In the original randomized phase III trials, the addition of 5FU to preoperative radiation tripled the pCR rate from 4–7% to 12–17% and reduced local recurrence [5, 6, 64]. The short half-life of 5FU supports the use of prolonged venous infusions of 5FU to radiosensitize every radiotherapy fraction. This method of delivery administers near to maximum doses with minimal toxicity. Hence, prolonged venous infusions of 5-fluorouracil or oral capecitabine are recommended rather than bolus 5FU [65, 66]. Capecitabine at a dose of 800–900 mg/m^2 twice daily for 5 days each week (Monday–Friday) of the 5-week radiation therapy is considered standard practice in many countries.

Irinotecan-Based Chemoradiation

Small initial phase II studies suggested irinotecan added to standard fluoropyrimidine-based CRT increased response rates [67, 68], but a randomized trial (RTOG0012) showed no benefit from a combination of weekly irinotecan to continuous infusional 5FU and concurrent radiation in 106 patients with T3–T4 distal tumours [69]. A current ongoing phase III randomized trial has randomized over 400 patients in the UK (ARISTOTLE) between capecitabine-based CRT, the same combination with concurrent weekly irinotecan in MRI-defined high-risk rectal cancer (www.controlled-trials.com/ISRCTN09351447).

Oxaliplatin-Based Chemoradiation

Early attempts in phase II trials to integrate oxaliplatin into fluoropyrimidine-based CRT showed promising results in terms of high rates of pCR. Consequently, five phase III trials (STAR-01, ACCORD 12/0405 PRODIGE 2, NSABP R-04, PETACC-6 and the CAO/ARO/AIO-04 study) [24, 66, 70–73] and two additional trials performed in China [35•, 74] were designed to add oxaliplatin to concurrent 5FU or capecitabine-based chemoradiotherapy. Most added oxaliplatin as a radiosensitizer (with low weekly doses, i.e. 50–60 mg/m^2 rather than systemically active doses of 85–130 mg/m^2). The results have been generally disappointing. In four out of five of these randomized phase III trials, the chemoradiation arm adding oxaliplatin was associated with a significant increase in grade 3–4 acute gastrointestinal toxicity [66, 70–73]

Two trials showed an increase in the pCR rate [24, 71], but in only one of these was the increase statistically significant [24]. Two trials suggest oxaliplatin may improve DFS [74, 75]. However, the design of the German trial is partly flawed by an inadequate control arm and the inclusion of oxaliplatin as postoperative adjuvant CT [75]. Hence, it is difficult to determine whether the preoperative chemoradiation component, the postoperative adjuvant component or both improve the DFS. Given the increase in toxicity without clear outcome benefit, concurrent oxaliplatin is not routinely recommended as an addition to fluoropyrimidine-based CRT outside clinical trials. Meta-analyses suggest oxaliplatin may increase pCR rates, but enhances acute toxicity [76].

Consolidation Chemotherapy after CRT/SCPRT

The introduction of additional chemotherapeutic agents such as oxaliplatin and irinotecan and the proven role of oxaliplatin in the adjuvant setting in colon cancer—plus a variety of targeted agents—have stimulated the use of neoadjuvant CT as an additional strategy to achieve systemic control. A long interval/delay after CRT has traditionally been recommended partly to allow the acute inflammatory and immunosuppressive effects of CT and RT to subside and lessen the risk of surgical complications. Additional systemic 'consolidation' CT before surgery could increase response rates and enable more patients to be managed nonoperatively. In series where radical surgery is performed after CRT, sequential additional courses of FOLFOX after chemoradiation increased the pCR rate from 18% with CRT alone and surgery performed at 8 weeks to 38% when six courses of FOLFOX were administered and surgery was performed at 19 weeks [77].

SCPRT followed by immediate surgery does not achieve tumour regression, but delayed surgery can result in substantial downstaging for patients with involvement of the MRF [78–80]. This longer interval has also been extrapolated to the use of SCPRT, which potentially allows the introduction of CT. An American study used SCPRT followed by 4 course of mFOLFOX6 in 44 evaluable patients (4 staged as cT4 and 40 as cT3) reported histopathological downstaging to ypT0-2 in 75% of patients and to ypT0 in 30% [54].

The Dutch Colorectal Group treated patients presenting with rectal cancer and synchronous resectable metastases with SCPRT followed by six cycles of capecitabine and oxaliplatin plus bevacizumab in the Dutch M1 phase II trial. Compliance to CT was very high and 90% received ≥4 cycles. In total, 36/50 (72%) of patients eventually underwent radical surgical treatment [81].

A randomised trial in patients with fixed cT3 or cT4 or locally recurrent rectal cancer showed this combination (SCPRT and FOLFOX) achieved a microscopically radical resection ie R0 (primary endpoint) resection rate of 77% and a 16% pCR rate with this schedule [17••].

This concept is tested in 'The Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation' (RAPIDO) trial [55]. The trial randomly assigned patients with more locally advanced rectal cancer to SCPRT followed by six cycles of oral capecitabine with intravenous oxaliplatin, and then TME vs. preoperative long-course CRT followed by TME and optional postoperative CT. Results are awaited.

Following neoadjuvant treatment (and prior to surgery), MRI can define different types of response (fibrous, desmoplastic and colloid), categorize histopathologic TN downstaging and accurately define a radiologic tumour regression grade (mriTRG). If sufficient downstaging/downsizing is confirmed, the surgeon may modify the initial treatment plan or even avoid surgery. In contrast, failure to respond can potentially be salvaged by additional CT at this point, prior to surgery, rather than waiting several months until surgery has taken place and the patient recovered sufficiently.

An alternative strategy is to alternate CT and RT. If RT when extended is susceptible to repopulation, integrating systemic CT between a split course of RT may minimize such repopulation [82].

Conclusions

Upfront therapy with CT alone or administered before or after CRT /SCPRT followed by surgery represents a rational way of treating LARC. Under- or overtreatment remains a potential problem, so optimal staging is necessary for accurate risk assessment. In middle third cT3 tumours with free MRF, CT alone has shown good efficacy in phase II studies. Its definitive role is being evaluated in phase III studies. In higher-risk patients, induction CT prior to CRT has not impacted adversely on local control and been associated with better compliance and lower toxicity. Given these advantages, this induction

strategy is now considered a new treatment alternative for patients with high-risk rectal cancer in some European institutions and the USA.

Following SCPRT or CRT with systemic 'consolidation' chemotherapy is a further rational approach which obeys De Ruysscher's Principle of SER (the interval between the start of treatment and the end of radiotherapy), which ideally should be as short as possible to avoid repopulation [83] In the RAPIDO trial, the SCPRT arm allows earlier administration of full systemic chemotherapy compared to CRT. Hence, results of this trial could change practice.

In addition, since metastatic disease is now the predominant cause of recurrence and death, many believe that systemic neoadjuvant CT might, in selected cases, substitute for CRT. However, any future results for neoadjuvant CT alone will need to be benchmarked against the outcomes with SCPRT and CRT in terms of R0 resection anastomotic leaks, failure to reverse a temporary colostomy and local recurrence.

Compliance with Ethical Standards

Conflict of Interest Carlos Fernandez-Martos and Alfonso Garcia-Fadrique declare that they have no conflict of interest. Rob Glynne-Jones has received research funding through grants from Roche and Merck Serono, has received speaker's honoraria from Roche, Amgen, Servier, Sanofi and Merck Serono and has received compensation from Eli Lilly, Roche, Home Nutrition, Servier, Sanofi, Eisai and Amgen for service on advisory boards.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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