Preoperative Treatment of Locally Advanced Rectal Cancer

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Abstract

The preoperative management of locally advanced rectal cancer has evolved over the years to establish fluoropyrimidine-based chemoradiation as the usual standard of care. With the advent of newer agents – chemotherapeutic and biologic – for treatment of colorectal cancer, their role in this setting is being evaluated as well. This review is focusing on up-to-date data and studies regarding preoperative treatment of locally advanced rectal cancer.

Keywords

Preoperative, chemotherapy, radiation therapy, rectal cancer, fluorouracil(5-FU), oxaliplatin, pathologic complete response, survival rate

Disclosure: The authors have no conflicts of interest to declare.
Received: 17 September 2012 **Accepted:** 1 October 2012 **Citation:** *European Oncology & Haematology*, 2012;8(4):224–7 *DOI: 10.17925/EOH.2012.08.4.224*
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Rectal cancer, as distinct from colon cancer, occurs in about 40,000 people annually in the US.[1] It is an adenocarcinoma, and surgical resection remains the only therapeutic modality offering a chance of cure. However, compared to cancers of the colon, rectal malignancies are more difficult to resect. The lack of a robust mesentery, coupled with the rectum's proximity to other genitourinary organs and the pelvic wall make complete surgical resection for T3-T4 and/or N1-N2 tumours difficult. For most stage I |(T1-T2, N0) disease (AJCC 7th Edition), complete surgical resection with clear margins usually suffices.[2,3] However, for locally advanced rectal cancer [hereby defined as some T2 tumours (low and/or anterior rectum) and most T3, T4 or N1-N2 disease], surgical resection alone is not sufficient.[2,3] Therefore, radiation and chemotherapy have evolved as important adjuncts in rectal cancer treatment, to allow better local outcomes. Over the years, the role of these adjunctive therapies has grown and various studies are available to guide therapy decisions.

Preoperative Radiation in Rectal Cancer

The first major randomised trial to evaluate adjunctive therapy for rectal cancer was the Swedish study – it compared preoperative radiation and surgery to surgery alone, and demonstrated improved local recurrence and overall survival with the addition of 25 Gy radiation preoperatively.[4,5] This was followed by the Dutch study, which also used 25 Gy radiation prior to total mesorectal excision (TME). Again, improved local recurrence rates were seen; early overall survival, however, was not affected.[6] These results, combined with the relatively easy radiation schedule and low treatment-related toxicities, led to preoperative radiation becoming an integral part of treatment of locally advanced rectal cancer.

Addition of 5-Fluorouracil to Preoperative Radiation

The next step in this process was the addition of concurrent chemotherapy to preoperative radiation. Fluoropyrimidines have been good radiation sensitisers and some notable randomised controlled trials done around the turn of the millennium tested their utility in locally advanced rectal cancer (see *Table 1*). The EORTC study randomised patients to four arms: one employed preoperative radiation alone, and the other three added 5-fluorouracil (5-FU) to radiation in various combinations. At five years, local recurrence rates were halved with the addition of 5-FU.[7] Again, overall survival remained unaffected. The Fédération Francophone de Cancérologie Digestive (FFCD) trial had only two arms, comparing preoperative chemoradiation to preoperative radiation alone, and demonstrated strikingly similar results. The addition of 5-FU led to the five-year local recurrence being halved, but with similar five-year overall survival.[8] Thus, the clinical utility of adding 5-FU to radiation therapy for rectal cancer was established. Then, the German Rectal Cancer Study Group trial demonstrated that preoperative therapy led to improved five-year local recurrence rate, compared to the same therapy being administered after surgery.[9] Thus, for the most part of the previous decade, fluoropyrimidine-based chemoradiation has been the standard of care for locally advanced rectal cancer. Recently published 11-year follow up data of the study showed a persisting significant improvement of pre- versus postoperative CRT on local control with local relapse was 7.1 versus 10.1 % (p=0.048). However, there was no clear overall survival effect with overall survival at 10 years of 59.6 versus 59.9 % (p=0.85). The 10-year cumulative incidence of distant metastases (29.8 and 29.6 %; p=0.9).[10] It indicates that more effective systemic treatment is important in the multimodal therapy for locally advanced disease.

Modifications of Preoperative 5-Fluorouracil-based Chemoradiation

Building on the 5-FU-based chemoradiation backbone, the addition of other agents is being evaluated in various trials. Capecitabine, the oral prodrug of 5-FU, has become an attractive alternative to the latter agent. It is at least as efficacious as 5-FU and its utility in the management of resected and metastatic colorectal cancer has been demonstrated in various clinical trials.[11–13] A recent published German randomised Phase III study compared capecitabine versus

Table 1: Notable Randomised Trials of Preoperative Therapy for Rectal Cancer*

Study	Years	Treatments	Pathologic Complete Response Rate	Local Recurrence Rate	Overall Survival
Swedish[5]	1987–90	RT → Sx	NA	9 %	38 %
		Sx		26 %	30 %**
Dutch[6]	1996–99	RT → Sx	NA	2.4 %	82 % each
		Sx		8.2 %	(two years)
EORTC 22921[7]	1993–2003	RT → Sx	NA	17 %	65 % each
		5-FU/RT → Sx		9 %	(five years)
		RT → Sx →5-FU		9 %	
		5-FU/RT → Sx → 5-FU		8 %	
FFCD 9203[8]	1993–2003	5-FU/RT → Sx	11.5 %	8 %	68 % each
		RT → Sx	3.5 %	16.5 %	(five years)
German[9]	1995–2002	5-FU/RT → Sx	NA	6 %	75 % each
		Sx → 5-FU/RT		13 %	(five years)
ACCORD12-Prodige2[24]	2005–8	5-FU/OxaliPt/RT → Sx	19 %	NA	NA
		5-FU/RT → Sx	14 %		
STAR-01[25]	2003–8	Cape/OxaliPt/RT → Sx	16 % each	NA	NA
		Cape/RT → Sx			
German[26]	2006–10	5-FU/OxaliPt/RT → Sx	17.5 %	NA	NA
		5-FU/RT → Sx	13 %		

**Results that are not statistically significantly different are combined for the arms, for simplicity. In addition, local recurrence rates are after the same follow-up time as the overall survival results. **These results are after a median follow-up of 13 years. Sx = surgery; RT = radiation therapy; 5-FU = 5-fluorouracil; NA = not available.*

5-FU in combination with radiation in 401 patients with stage II–III rectal cancer as adjuvant/neoadjuvant settings.[14] The results showed five-year overall survival in the capecitabine group was non-inferior to that in the 5-FU group (76 versus 67 %; p=0.0004; post hoc test for superiority p=0.05). Three-year disease-free survival was 75 % (95 % CI 68–81) in the capecitabine group and 67 % (59–73) in the 5-FU group (p=0.07). The numbers of patients who had local recurrences were similar in each group (12 [6 %] in the capecitabine group versus 14 [7 %] in the fluorouracil group, p=0.67). However, there were fewer patients developed distant metastases in the capecitabine group (37 [19 %] versus 54 [28 %]; p=0.04). The authors concluded 'Capecitabine could replace fluorouracil in adjuvant or neoadjuvant chemoradiotherapy regimens for patients with locally advanced rectal cancer.' In practice, capecitabine is commonly applied in clinic practice as alternative for 5-FU in combining with radiation.

The other major advance in the management of colorectal cancer has been the use of oxaliplatin. Oxaliplatin is the third platinum compound – after cisplatin and carboplatin – to gain a significant role in cancer chemotherapy. By forming platinum-DNA adducts, it achieves tumour cell kill.[15,16] It has been tested widely in the treatment of resected and metastatic colorectal cancer and several randomised controlled trials have shown that in combination with an oral or intravenous fluoropyrimidine, oxaliplatin achieves improved clinical outcomes.[17-24] Based on these findings, oxaliplatin has been added to fluoropyrimidine-based preoperative chemoradiation for locally advanced rectal cancer. A major randomised Phase III study conducted in France (ACCORD 12/0405 PRODIGE 2) tested the addition of oxaliplatin to the standard preoperative chemoradiation approach using capecitabine.[24] Patients with T2 (low or anterior), T3 and T4 rectal cancers, with any N and M0 status were enrolled; this staging was confirmed by either endorectal ultrasound or magnetic resonance imaging (MRI). Patients were randomised to either capecitabine, oxaliplatin and radiation (50 Gy), or capecitabine and radiation (45 Gy). Preoperative treatment was tolerated well: the major grade III/IV toxicity differences were the higher incidence of diarrhoea (12.5 versus 3 %, grade III/IV) and fatigue (5 versus 0.8 %, grade III) in the experimental arm. However, as is noted by the authors of the study as well, it is difficult to see if these toxicities were higher due to the oxaliplatin or the higher radiation dose. Surgical outcomes were very good and well-balanced: 98 % of patients in each arm went to surgery, after a median interval of six weeks since chemoradiation completion. The majority of patients (70 %) had low anterior resection (LAR) and 75 % were spared a permanent stoma – in each arm. The 60-day postoperative mortality was very low – 0.3 % in each arm. The primary outcome was pathologic complete response (ypCR). Using historical data, ypCR of 11 % was expected in the control arm[8] and an improvement to 20 % in the experimental arm was the stated goal. However, this outcome was not met. Although an improvement from 14 to 19 % was seen, the difference was not statistically significant. It should be noted that node-positive disease remained in only 30 % of cases, down from 72 % based on preoperative assessment. Nonetheless, based on the statistically non-significant change in the primary outcome of the study, the authors concluded that oxaliplatin should not be used for preoperative chemoradiation for locally advanced rectal cancer.[25]

Another large randomised study testing the addition of oxaliplatin to preoperative 5-FU-based chemoradiation was conducted in Italy.[26] Locally advanced rectal cancer (either T3-4 or N1-2 disease) was required; approximately 750 patients were enrolled. Randomisation was to 5-FU, oxaliplatin and radiation, or 5-FU and radiation. Preoperative treatment was well-tolerated; diarrhoea (15 versus 4 %) and asthenia (3 versus 0 %) were more frequent grade III toxicities in the experimental arm. Approximately 80 % of patients in each arm were spared abdominoperineal resection and 60-day surgical mortality was less than 1 % in each arm. The primary outcome of the study is overall survival; pathologic complete response was a pre-specified outcome. The ypCR was 16 % in each arm. Intra-abdominal metastases at the time of surgery were detected in fewer patients in the oxaliplatin arm (0.5 versus 2.9 %). However, the authors of the study concluded very carefully as 'Adding oxaliplatin to fluorouracil-based preoperative chemoradiotherapy significantly increases toxicity without affecting primary tumour response. Longer follow-up is needed to assess the impact on efficacy end points.

A third study, from Germany, also tested the addition of oxaliplatin to standard 5-FU-based chemoradiation.[27] Approximately 640 patients with locally advanced rectal cancer were randomised to 5-FU, oxaliplatin and radiation, or standard 5-FU and radiation. Preoperative treatment was completed in 74 and 97 % of patients; grade III/IV toxicities occurred in about 22 % of patients in each arm. Abdominoperineal resection was needed in only 12 % of patients in each arm; postoperative complications were no different. Pathologic complete response, a pre-specified secondary outcome, was seen in 17.6 versus 13.1 % (p=0.033), of patients, meeting pre-specified statistical significance criteria. The study concluded that adding oxaliplatin to 5-FU based XRT was well tolerated and associated with increased pCR rate. However, longer follow-up is necessary to evaluate the primary endpoint of the study, disease-free survival. Formal publication is awaited.

Should Oxaliplatin be Used for Preoperative Chemoradiation?

This is the obvious question that remains. At first glance, based on the early results discussed above, there is no remarkable improvement in pathologic complete response. However, the long-term outcomes of local recurrence rate and overall survival are awaited. These outcomes are clinically more significant. As mentioned above, the survival advantage conferred by the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy for resected colorectal cancer has been well-established.[17,18,22] In fact, 35 % of patients in the NSABP C-07 trial had cancer of the recto-sigmoid colon.[22] Thus, oxaliplatin may have an important role in securing better long-term outcomes in resected rectal cancer. Based on the available data, it seems the role of oxaliplatin in the neoadjuvant setting is still controversial with moderate increased pCR rate but not impressive as expected and moderately increased toxicity as well. It may not ready as a general recommendation to add oxaliplatin in preoperative therapy regimens yet, which means fluoroprimidine alone with chemoradiation is still considered current 'standard' regimen. However, we are waiting for the data regarding disease-free survival and overall survival rates for these Phase III studies.[25,27] Interestingly, a follow up analysis of the French study (ACCORD 12/0405 PRODIGE 2) showed ¼ of patients on the study were 70 years or older and their tolerability to the chemoradiation was not as good as that of younger patients, which suggested that appropriate therapeutic schedule/regimen needs be considered.[28]

Should we reserve it for adjuvant therapy, then? The idea behind preoperative therapy is to improve surgical outcomes, but to also deliver therapy upfront as it is better tolerated (than when given postoperatively) and early institution of systemic therapy may achieve better distant disease control. If the bulk of chemotherapy is reserved for the postoperative setting, there is a significant delay in delivering treatment. After completion of preoperative treatment, a recovery period of 4–6 weeks is followed by surgery, which is again followed by a recovery period of 4–6 weeks before adjuvant therapy can be started. Therefore, 2–3 months elapse without any chemotherapy, and if oxaliplatin is reserved for the adjuvant setting only, then the patient will be administered this agent only after 14–18 weeks since treatment initiation. In addition, due to morbidity from surgery, tolerance of therapy is lower compared to its administration preoperatively. This has been demonstrated in the German rectal cancer trial[9] and has been consistently seen in therapy for upper gastrointestinal tract tumours, where preoperative therapy is completed by more than 90 % of patients in large studies, whereas less than half are able to complete postoperative therapy.[29] More recently, in a randomised Phase II study comparing preoperative induction chemotherapy and chemoradiation to the standard approach of preoperative chemoradiation followed by surgery and adjuvant chemotherapy, for locally advanced rectal cancer, immediate surgical outcomes were similar, but there was improved chemotherapy completion and lower toxicity when all the therapy was done prior to surgery.[30] Again, only half the patients completed therapy in the postoperative group whereas 92 % completed therapy when all of it was given preoperatively. In another Phase II study evaluating intensification of preoperative therapy, chemotherapy with capecitabine and oxaliplatin was instituted, followed by capecitabine-based chemoradiation and then total mesorectal excision. A 20 % pathologic complete response rate and 83 % three-year overall survival were seen[31] These results indicate that the earlier institution of oxaliplatin may offset the increased toxicity by improving treatment completion rates, thus ultimately achieving better long-term outcomes.

Conclusion

The standard of care for locally advanced rectal cancer remains fluoropyrimidine (5-FU or capecitabine) based preoperative chemoradiation. The role of oxaliplatin in preoperative chemoradiation of rectal cancer will become clearer once long-term data from large randomised trials discussed above are available. In addition, trials evaluating molecular agents that target key signalling pathways in colorectal cancer are being conducted and may lead to therapeutic breakthroughs [NCT00611858, NCT01443377, NCT00686166, NCT01263171, NCT01426074]. ■

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