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GASTROINTESTINAL CANCERS (J MEYER, SECTION EDITOR)

Role of Chemotherapy in the Neoadjuvant/Adjuvant Setting for Patients With Rectal Adenocarcinoma Undergoing Chemoradiotherapy and Surgery or Radiotherapy and Surgery

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Abstract
Rectal cancer has been successfully managed in the last couple of decades. In the USA, as the initial approach, neoadjuvant concurrent chemoradiation has been associated not only with decrease in tumor size and recurrence but also with higher resection rate with minimal side effects. Data support that addition of chemotherapy to radiotherapy is superior to radiotherapy alone in the neoadjuvant setting. Recent debates have addressed the question of administration of adjuvant chemotherapy following surgery. In this article, we discuss the role of chemotherapy in both the neoadjuvant and the adjuvant settings for locally advanced rectal cancer.

Keywords Colorectal cancer · Rectal cancer · Locally advanced rectal cancer · Neoadjuvant chemoradiation · Adjuvant therapy

Introduction

Colorectal cancer is the third leading cause of death related to cancer in the USA. In 2017, the estimated new cases of and deaths from colorectal cancer were 135,430 and 50,260 respectively [1]. According to the "Cancer Facts and Figures 2016," the data suggests that there would be an estimated 39,220 new cases of rectal cancer for both sexes in the USA in 2016 [2]. Although colorectal cancer has been considered to be a major cancer, its trend has been declining in the last decade. This decline is based on risk factor modifications and use of preventive measures like colonoscopy for early detection [2].

Like most cancers, the treatment strategy for rectal cancer is stage-dependent. Important staging and prognostic factors for rectal cancer are the depth of invasion, location from the sphincter, status of the circumferential margin, and the involvement of locoregional lymph nodes or neighboring organs [3].

The management of rectal cancer is multimodal and may require interdisciplinary involvements that include pathology, medical oncology, surgical oncology, and radiation oncology depending on the stages of the disease. Locally advanced rectal cancers (T3/T4 or N1/N) have been difficult to manage merely by surgery due to the confinement of the bony pelvis and the requirement not to damage the autonomic nerves.

Pretreatment Clinical Staging and Stratification of Patients Based on Risk Groups

Any cancerous lesion present within 12 cm of the anal verge by rigid proctoscopy is considered rectal cancer. According to the NCCN (National Comprehensive Cancer Network), patients with T3/4N0 cancer (stage II) or TanyN+ (stage III) are considered high-risk groups for locoregional recurrence. A difference is seen in the ESMO (European Society for Medical Oncology) guidelines, which include patients diagnosed with T3/T4b cancer with invasion to mesorectal fascia and/or metastatic iliac node(s) [4].

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Treatment Plans and Controversies for Stage II (T3/4 and Negative Locoregional Node[s]) and III (Positive Locoregional Node[s] Without Distant Metastasis) Rectal Cancers

Currently in the USA, the following treatment options are available for locally advanced rectal cancer:

- Preoperative long-course chemoradiation or short-course radiation therapy without concurrent chemotherapy
- Surgery
- Postoperative chemo or combined chemoradiation therapy

The NCCN guidelines recommend neoadjuvant long-term chemoradiation (radiation dose of 45–50.4 Gy in 25–28 fractions with multiple radiation fields) and adjuvant chemotherapy, while the ESMO guidelines suggest neoadjuvant short-course chemoradiation (25 Gy in 5 fractions) or long-course chemoradiation, and adjuvant chemotherapy (optional) [5]. According to a Polish randomized trial, higher rates of complete response were observed in groups receiving long-term chemoradiation than in short-term treatment [6], although patients undergoing short-course radiation alone underwent surgery following the neoadjuvant treatment at an earlier time point compared to patients in the long-course arm. The study also demonstrated that long-course chemoradiation was responsible for more acute toxicities than the short-course regimen (18.2 vs 3.2% respectively), with similar rates of late toxicities.

Traditional Neoadjuvant Chemoradiation

Neoadjuvant combined modality (chemoradiation, CRT) therapy is a standard of care for locally advanced (stages II and III) rectal cancers. Improved pathological complete response (pCR) and locoregional control due to concurrent neoadjuvant chemoradiation (as opposed to radiation alone) have been documented in past studies. Important studies regarding concurrent chemoradiation therapy for locally advanced rectal cancer are illustrated in Table 1.

The NSABP R-03 study (Table 1) included 267 patients with clinically staged T3 or T4 or node-positive rectal cancer. Though the study showed that there was significant 5-year disease-free survival improvement for the preoperative chemoradiation group compared to the postoperative chemoradiation group, no statistical difference was observed in terms of 5-year OS (overall survival) for the same group (preoperative 74.5% vs postoperative 65.6%, $p = 0.065$).

In the EORTC 22921 study, patients clinically staged having T3 or T4 resectable cancer were randomly assigned into different groups receiving preoperative radiotherapy, preoperative chemoradiotherapy, preoperative radiotherapy and postoperative chemotherapy, or preoperative chemoradiotherapy and postoperative chemotherapy. The chemotherapy regimen included 5-FU/leucovorin, and radiotherapy consisted of 45 Gy given over 5 weeks. The study concluded that both adjuvant and adjuvant chemotherapy improved local control of the disease. After a median follow-up of 10.4 years, the long-term analyses showed no difference between the neoadjuvant chemoradiation and neoadjuvant radiotherapy groups with respect to 10-year overall survival (50·7 vs 49.4%, $p = 0.91$) [13].

In the follow-up of the German CAO/ARO/AIO-94 study published in 2012, the data did not show any significant difference for 10-year overall survival (Table 1) with a median follow-up of 134 months. But the study demonstrated a favorable 10-year cumulative incidence of local relapse for the neoadjuvant group over the adjuvant group (7.1 vs 10.1%, $p = 0.048$).

Table 1 Important studies of neoadjuvant chemoradiation or radiotherapy for locally advanced rectal cancer

Study	Population	Outcome analyses		Ref.
		pCR (pathological complete response) %	5- or 10-year DFS (disease-free survival, in %)	
EORTC22921, 2006	Neoadjuvant chemoradiation ($n = 505$) vs neoadjuvant radiotherapy ($n = 506$)	14 vs 5.3 ($p = 0.05$)	58.2 vs 52.2 (5 years)	[7]
FFCD9203, 2006	Neoadjuvant chemoradiation ($n = 375$) vs neoadjuvant radiotherapy ($n = 367$)	11.4 vs 3.6 ($p = 0.001$)	67.4 vs 66.9 ($p = 0.684$) (5 years)	[8]
NSABP-R03, 2009	Neoadjuvant chemoradiation ($n = 123$) vs adjuvant chemoradiation ($n = 131$)	N/A	64.7 vs 53.4 ($p = 0.011$) (5 years)	[9]
CAO/ARO-094, 2012	Neoadjuvant chemoradiation ($n = 404$) vs adjuvant chemoradiation ($n = 395$)	N/A	68.1 vs 67.8 ($p = 0.65$) (10 years)	[10•]
Spanish GCR-3	Neoadjuvant chemoradiation and adjuvant chemotherapy ($n = 52$) vs induction chemotherapy followed by neoadjuvant chemoradiation ($n = 56$)	N/A	64.3 vs 60.7 ($p = 0.73$) (5 years)	[11••]
Sweden Braendengen, 2008	Neoadjuvant chemoradiation ($n = 98$) vs neoadjuvant radiotherapy ($n = 109$)	16 vs 7 ($p = 0.04$)	63.0 vs 44.0 ($p = 0.003$) (5 years)	[12]

Table 2 Studies to demonstrate the role of adjuvant chemotherapy in patients with locally advanced rectal cancer

Study	Population	Outcome analyses 5- or 10-year DFS (disease-free survival, in %)	Ref.
DCCG, 2015	Observation ($n = 221$) vs adjuvant chemotherapy ($n = 216$)	79.2 vs 80.4 ($p = 0.73$) (5 years)	[18]
Chronicle, 2014	Observation ($n = 59$) vs adjuvant chemotherapy ($n = 54$)	88.0 vs 89.0 ($p = 0.75$) (3 years)	[19]
I-CNR, 2014	Neoadjuvant chemoradiation ($n = 310$) vs neoadjuvant chemoradiation and adjuvant chemotherapy ($n = 324$)	70.0 vs 69.1 ($p = 0.772$) (5 years)	[20]

The FFCD study compared preoperative radiotherapy with preoperative concurrent chemoradiation (5-FU/LV) (Table 1). In terms of sphincter preservation, no significant difference was observed between the groups. It was also evident that both arms were non-significant for 5-year progression-free survival (PFS) (55.5% for radiotherapy group vs 59.4% for chemoradiation group, $p = 0.684$).

Finally, the long-term update for the Spanish GCR-3 study demonstrated similar outcomes for both the adjuvant group and non-adjuvant group in terms of 5-year DFS with a median follow-up of 69.5 months (64.0 vs 62.0% respectively, $p = 0.85$) [14]. The study also showed no significant difference between the groups for 5-year OS (78.0 vs 75.0% respectively, $p = 0.64$).

Splitting of Treatment With Short Induction Chemotherapy

The principle objective of splitting the treatment around the targeted surgical treatment has been to reduce the locoregional recurrence of locally advanced rectal cancer while limiting the number of chemotherapy cycles before the surgery and then delivering remaining cycles after the surgery [15–17].

Calvo et al. (2006) concluded that short-course induction of intense chemotherapy with FOLFOX 4 statistically improved the pathologic complete response with tegafur-sensitized preoperative chemoradiation (compared to chemoradiation alone in a historical cohort) [13]. A similar conclusion was evident by Schou et al. (2012) [17]. The study found that 94% of the patients who received induction therapy with CAPOX for 2 weeks before concurrent neoadjuvant chemoradiation experienced R0 resection during TME, and 69% were downstaged for the T stage. However, according to Marechal et al. (2012), outcomes with induction chemotherapy were not associated with favorable locoregional impact on traditional therapy [16]. In the USA, induction chemotherapy before the standard neoadjuvant concurrent chemoradiation is not recommended for locally advanced rectal cancer.

Adjuvant Treatment Controversy

The current standard of care for adjuvant chemotherapy for locally advanced rectal cancer in the USA, including for patients who received preoperative chemoradiotherapy, includes FOLFOX (5-FU, leucovorin, and oxaliplatin) or CAPEOX (capecitabine and oxaliplatin). The major role of adjuvant chemotherapy has been to eliminate micrometastatic disease.

There has been much attention to the necessity for adjuvant chemotherapy for the patients who have already received neoadjuvant chemoradiation and TME afterward. To discuss further, the long-term follow-up of the EORTC 22921 study concluded that after a median follow-up of 10.4 years, no statistically significant differences were present between the groups who had received adjuvant therapy and those who had not in terms of OS (51.8 vs 48.4%; HR = 0.91, 95% CI = 0.77 to 1.09, $p = 0.32$), DFS (47.0 vs 43.7%; HR = 0.91, 95% CI = 0.77 to 1.08, $p = 0.29$), or distant metastasis ($p = 0.22$) [13]. The study does not recommend the administration of adjuvant chemotherapy after preoperative radiotherapy with or without chemotherapy. Poor adherence to adjuvant therapy is one explanation for this result.

Table 2 shows the results of three other studies (DCCG, Chronicle, and I-CNR) which also investigated the role of adjuvant chemotherapy for patients treated with neoadjuvant chemoradiotherapy and surgery. According to these studies, no significant differences were observed in terms of 3–5-year DFS. According to the Dutch Colorectal Cancer Group (DCCG) (2015) trial, 5-year cumulative locoregional recurrence rate was 7.8% for both the observation and the treatment groups. The I-CNR (2014) study also showed that no clinical significance was demonstrated in terms of distant metastases between the follow-up and the neoadjuvant groups.

Conclusion

Despite the recent controversies, the practice neoadjuvant chemoradiation and adjuvant chemotherapy with or without radiation following a definitive surgery have been a standard for locally advanced resectable rectal cancer in the USA. But, it has not yet been demonstrated optimally whether the intensification of chemotherapy will modify the outcomes. Finally, the management of locally advanced rectal cancer requires multidisciplinary collaborations and appropriate risk stratification, and treatment should be designed on individual basis.

Compliance with Ethical Standards

Conflict of Interest Shahab Ahmed and Cathy Eng declare that they have no conflict of interest.

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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