Neoadjuvant Chemotherapy First, Followed by Chemoradiation and Then Surgery, in the Management of Locally Advanced Rectal Cancer

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Abstract

Standard therapy for locally advanced rectal cancer (LARC) is preoperative chemoradiotherapy and postoperative chemotherapy. At Memorial Sloan-Kettering Cancer Center (MSKCC) the authors began offering FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) as initial treatment for patients with high-risk LARC to target micrometastases while treating the primary tumor. The purpose of this study is to report the safety and efficacy of initial FOLFOX given before chemoradiotherapy on tumor downsizing and pathologic complete response (pathCR) in LARC. The records of patients with stage II/III rectal cancer treated at MSKCC between 2007 and 2012 were reviewed. Of approximately 300 patients with LARC treated at MSKCC, 61 received FOLFOX as initial therapy. Of these 61 patients, 57 received induction FOLFOX (median 7 cycles) followed by chemoradiation, and 4 experienced an excellent response, declined chemoradiation, and underwent total mesorectal excision (TME). Twelve of the 61 patients did not undergo TME: 9 had a complete clinical response (CCR), 1 declined despite persistent tumor, 1 declined because of comorbidities, and 1 developed metastatic disease. Among the 61 patients receiving initial FOLFOX, 22 (36%) had either a pathCR (n=13) or a CCR (n=9). Of the 49 patients who underwent TME, all had R0 resections and 23 (47%) had tumor response greater than 90%, including 13 (27%) who experienced a pathCR. Of the 28 patients who received all 8 cycles of FOLFOX, 8 experienced a pathCR (29%) and 3 a CCR (11%). No serious adverse events occurred that required a delay in treatment during FOLFOX or chemoradiation. FOLFOX and chemoradiation before planned TME results in tumor regression, a high rate of delivery of planned therapy, and a substantial rate of pathCRs, and offers a good platform for nonoperative management in select patients. (*J Natl Compr Canc Netw* 2014;12:513–519)

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Modern therapy for locally advanced rectal cancer (LARC), with the combination of preoperative chemoradiotherapy and improved surgical techniques, has led to significant improvements in local disease control. Distant recurrence rates now exceed those of local recurrence.[1,2] The current standard management for stage II (T3/T4N0) and stage III (TanyN1/N2) rectal cancer is neoadjuvant chemoradiotherapy, followed by surgery, with 4 months of adjuvant systemic chemotherapy given at the end.[1,2] Although neoadjuvant chemoradiotherapy has been shown to decrease the incidence of local recurrence, overall survival and the risk of distant metastases have not been shown to be impacted by radiation therapy.[3,4]

Advances in systemic chemotherapy with the addition of oxaliplatin to 5-fluorouracil (5-FU) have resulted in improved survival in patients with metastatic colorectal cancer and those with stage III colon cancer treated with adjuvant FOLFOX (5-FU, leucovorin, oxaliplatin).[5–8] Response rates for patients with metastatic colorectal cancer treated with modern chemotherapy regimens such as FOLFOX have routinely exceeded 40% to 50%.[5,6] Furthermore, data suggest that the primary tumor may in fact be more sensitive to systemic chemotherapy compared with metastases.[9,10]

Thus, with the improvements in systemic therapy, several theoretical considerations now favor the use of upfront chemotherapy in patients with LARC. Of primary importance in the high-risk rectal cancer population is that current rectal cancer treatment paradigms do not deliver optimal combination systemic chemotherapy for approximately 3 to 4 months after initiation of neoadjuvant chemoradiotherapy, and this delay is theoretically disadvantageous because it allows a window for the growth of distant micrometastases that may already exist. Best systemic therapy given early offers the potential to optimally treat micrometastatic disease. Initial chemotherapy also permits delivery of treatment directly to the primary tumor while it has a fully intact vasculature, undisrupted by radiation or surgery. Finally, there is the practical consideration that completion of all planned treatment before surgery allows patients requiring a temporary diverting ostomy to avoid the challenges of undergoing chemotherapy in the presence of an ostomy. It also decreases the duration of temporary ostomies (to as little as 8 weeks) when no postoperative chemotherapy is planned.

These considerations, plus favorable data from preliminary reports exploring this strategy,[10–12] provide a solid rationale for shifting systemic treatment to earlier in the treatment paradigm. Based on these data, the authors began altering the sequence of treatment for most patients with LARC at Memorial Sloan-Kettering Cancer Center (MSKCC), offering patients initial chemotherapy with FOLFOX followed by chemoradiotherapy and then total mesorectal excision (TME). This article reports on the initial efficacy results of this approach and the associated toxicities.

Patients and Methods

A waiver of authorization was obtained from the MSKCC Institutional Review Board to review the records of all patients with LARC. A computerized search was then performed of all patients with newly diagnosed clinical stage II/III rectal cancer (T3/4N1–2 based on endorectal ultrasound or MRI) who had been treated with initial chemotherapy followed by chemoradiation at MSKCC between 2007 and 2012. Patients were chosen based on the treating physician's comfort with the regimen and patient agreement. Initially, the treatment was offered preferentially to patients with large bulky tumors who were thought to be at increased risk for metastatic disease. As comfort with the regimen grew, however, the treatment began to be offered to patients with stage II or III disease. Of the 61 patients in this cohort, 42 were treated in 2011 and 2012.

Patients received standard mFOLFOX6 chemotherapy administered every 2 weeks. Two patients refused mediports: one received CapeOx (capecitabine plus oxaliplatin), and the other received the FLOX regimen with weekly bolus 5-FU and oxaliplatin every 2 weeks.[13,14]

Monitoring During Induction Chemotherapy

All of the patients were assessed with interval imaging, either with MRI or endorectal ultrasound, for response or progression before initiation of radiation. Most were reimaged after approximately 4 to 6 cycles.

Chemoradiotherapy

Radiation therapy was administered approximately 2 to 3 weeks after the last planed dose of induction chemotherapy with standard fractionation using either concurrent infusional 5-FU at 225 mg/m^2 continuously throughout radiation, or capecitabine, 825 mg/m^2 twice daily, Monday through Friday during radiotherapy.

All patients underwent CT simulation in the prone position. The gross tumor volume (GTV) consisted of the primary tumor and enlarged regional lymph node, and the clinical target volume (CTV) consisted of the GTV, rectum, and lymph node regions, including mesorectum, presacral nodes, internal iliac nodes, and superior rectal nodes. The initial planning target volume (PTV) was an expansion of approximately 5 mm on the CTV to account for daily setup error and organ motion. For the boost fields, a CTV boost consisted of the GTV, adjacent mesorectum, and presacral space, and the PTV boost consisted of a 0.5-cm expansion of the CTV boost. Patients underwent either 3-dimensional conformal (3DCRT) or intensity-modulated radiotherapy (IMRT) treatment planning with the in-house planning software. 3DCRT plans consisted of 3 or 4 orthogonal beams for the pelvic fields, and 2 lateral beams and 1 posterior-anterior beam for the boost fields. The PTV was treated to 45 Gy in 1.8-Gy fractions followed by a 5.4-Gy boost to the PTV boost to a total dose of 5040 cGy. IMRT plans consisted of 5 to 7 equally spaced coplanar fields. The patients treated with IMRT received 45 Gy in 1.8-Gy fractions to PTV and 50 Gy in 2-Gy fractions to the PTV boost as an integrated boost.

Surgery

Patients undergoing surgery underwent TME within 6 to 8 weeks after completion of chemoradiation at MSKCC. The surgery was performed by 1 of 6 colorectal surgeons who specialized in TME for rectal cancer. The choice of surgical procedure, either abdominoperineal resection or low anterior resection, was at the surgeon's discretion. Complete clinical response (CCR) was defined as no visible tumor on endorectal ultrasound or imaging with CT or pelvic MRI.

Pathologic Assessments

After TME, tissue specimens were evaluated using standard pathologic guidelines. In cases of residual macroscopic tumor, standard pathologic examination was performed on 3 to 5 sections to investigate the deepest invasion in the bowel wall. If no macroscopic tumor was present and only a small ulcer was observed, the ulcer with a 2-cm margin was examined for residual tumor and deepest invasion in the bowel wall. All lymph nodes were examined according to standard procedures, and the circumferential resection margin was measured.[15] Pathologic complete response (pathCR) was defined as the complete disappearance of all tumor cells.

Results

Patient Characteristics

Of approximately 300 patients with rectal cancer treated between 2007 and 2012 at MSKCC and its regional sites, 61 received some or all of their planned chemotherapy as the initial treatment of their LARC. The median age was 52 years, and 28 patients were women and 33 were men. The ECOG performance status in all patients was either 0 or 1. The most frequent endorectal ultrasound staging was uT3N1. Patient characteristics are summarized in Table 1.

Table 1 Patient Characteristics (N=61)

Baseline Characteristics	n
Sex	
Male	33 (54%)
Female	28 (46%)
Average age (range)	52 y (25–82 y)
ECOG performance status	
0	42 (69%)
1	18 (31%)
Stage at initial diagnosis[a]	
T3N0	7 (8%)
T3N1	24 (43%)
T3N2	23 (39%)
T4N0	1 (2%)
T4N1	4 (6%)
T4N2	2 (4%)

[a]According to staging by MRI or endorectal ultrasound.

Induction Chemotherapy Administration and Toxicities

Of the 61 patients who received some or all of their planned chemotherapy, 28 received a full 8-cycle course of initial chemotherapy with 5-FU and oxaliplatin. The median number of cycles was 7 (range, 2–12). Notably, because this was not a prospective study, there was no prespecified treatment plan. Therefore, some patients received their FOLFOX treatment at split times (ie, before and after surgery), and the number of cycles of chemotherapy varied. However, all patients, including those who declined surgery or radiation, received at least 8 cycles of FOLFOX. More recently, the intent has been to deliver the full course of planned chemotherapy upfront, without interruption. Of the 42 patients treated in 2011 and 2012, a total of 30 received all of their FOLFOX before chemoradiation.

The most common grade 1/2 toxicities with FOLFOX were fatigue (58%), nausea (32%), and neutropenia (25%). The most common grade 3 toxicities were diarrhea (4%), fatigue (1%), nausea (1%), and neutropenia (1%). These were managed with dose reductions and growth factor support. No grade 4 toxicities or serious adverse events requiring a break in treatment occurred (Table 2).

Table 2 Chemotherapy Toxicities Associated With Induction FOLFOX

Toxicity	Grade 1	Grade 2	Grade 3
Fatigue	28	5	1
Nausea	16	2	1
Diarrhea	3	2	2
Neutropenia	4	10	1
Vomiting	3	1	0
Anemia	7	0	0
Thrombocytopenia	13	0	0
Oral mucositis	1	1	0
Neuropathy	2	3	0

Chemoradiotherapy Administration and Toxicities

Of the 61 patients treated with initial chemotherapy, 4 who experienced an excellent response to initial FOLFOX chemotherapy declined radiation and proceeded directly to TME surgery. Of these, 2 had a pathCR. In the 57 patients who received pelvic radiation, no grade 4 toxicities or serious adverse events requiring a break in treatment occurred. Thus, all patients were able to complete chemoradiation without interruption. The most common grade 1/2 toxicities were fatigue (81%), diarrhea (64%), dermatitis (60%), and proctitis (53%). The grade 3 toxicities were diarrhea (2%), dermatitis (2%), and neutropenia (2%; Table 3).

Surgery and Surgical Morbidity

Among the 61 patients treated with initial chemotherapy, 12 did not undergo surgery. Of these, 9 had a CCR and elected to be managed nonoperatively; 1 refused recommended surgery despite incomplete tumor regression, and 1 had surgery deferred because of medical comorbidities. One patient developed liver metastases during treatment despite a significant regression of the primary tumor. Of the 49 patients who underwent surgery, all had a TME procedure with R0 resections. One patient had a wound infection requiring antibiotics, 2 had pelvic abscesses requiring drainage, and 1 had an anastomotic leak requiring reoperation. No postoperative mortalities occurred. Of the patients who had all 8 cycles of induction chemotherapy, 15 had temporary ostomies, which were reversed at a median time of 93 days (range, 62–179 days).

Pathologic and Clinical Response to Therapy

Of the 61 patients treated with initial chemotherapy, 22 (36%) had either a pathCR (n=13) or a CCR (n=9), the latter of which were treated with nonoperative management. Of the 49 patients who underwent resection, 23 (47%) had tumor response greater than 90%, including 13 (27%) who experienced a pathCR. Furthermore, 46 patients had node-positive disease (ultrasound or MRI TxN1/2), and 30 (65%) were downstaged to ypN0. Table 4 lists the clinical and pathologic staging.

Table 3 Chemoradiotherapy Toxicities Associated With Chemoradiation

Toxicity	Grade 1	Grade 2	Grade 3
Neutropenia	1	2	1
Dermatitis	25	7	1
Diarrhea	26	8	1
Fatigue	39	4	0
Proctitis	21	7	0
Cystitis	10	1	0
Nausea	8	0	0
Oral mucositis	9	1	0
Anemia	6	2	0
Thrombocytopenia	9	0	0

The median follow-up from the start of induction chemotherapy of all patients is 17.8 months (range, 69.0–10.7 months). Of the 61 patients, 5 have developed recurrent metastatic disease; 1 underwent resection of an isolated lung metastasis, 3 remain alive with unresectable metastatic disease, and the fifth developed a second primary colon cancer with liver metastases. Of the 28 patients who received all 8 cycles of initial FOLFOX, 8 experienced a pathCR (29%) and 3 experienced a CCR (11%) and have been managed nonoperatively. Notably, none of the 61 treated patients experienced progression of the primary tumor while receiving initial chemotherapy or subsequent chemoradiotherapy. All of the patients showed clinical regression of the primary tumor on proctoscopic examination and/or MRI. Of the 49 patients who underwent TME, all but 2 achieved pathologic downstaging. The 2 who did not change staging remained at T3N2, but did show clinical regression on endorectal ultrasound and a 20% to 40% treatment effect in the tumor. Notably, both of these patients had tumors with factors associated with a negative prognosis for response: one had Lynch syndrome and the other had a signet ring cell adenocarcinoma.[16,17]

Of 12 patients who did not undergo TME, 9 had a CCR (no residual cancer on examination or imaging studies) and were followed closely. One patient experienced local recurrence 6 months after completion of therapy and underwent transanal resection of a ypT1Nx adenocarcinoma. One patient underwent resection 7 months after completion of therapy because of clinical concern for local recurrence; however, the pathology revealed atypical cells with no overt evidence of carcinoma. The remaining 7 patients continue on active surveillance and remain disease-free with a median follow-up of 15.5 months (range, 47.6–10.7 months). The treatment schema and results are summarized in Figure 1.

Discussion

The concept of neoadjuvant initial chemotherapy before radiotherapy in LARC was first explored in

Table 4 Clinical and Pathologic Staging (N=49)

Initial Staging	Pathologic Staging								
	ypT0N0	ypTisN0	ypT1N1	ypT2N0	ypT2N1	ypT3N0	ypT3N1	ypT3N2	ypT4N0
cT3N0	1			3					
cT3N1	5			6	1	6	2		
cT3N2	4	1	1	5		3	2	3	
cT4N1	2						1		1
cT4N2	1						1		

a clinical trial by Chau et al,[11,18] which showed an 88% objective tumor control rate with neoadjuvant capecitabine/oxaliplatin. In a single-institution trial that began in March 2007 at MSKCC, 32 patients with clinical stage II or III rectal cancer were treated with neoadjuvant FOLFOX plus bevacizumab, without planned radiation therapy unless clinical progression was noted. All patients experienced tumor regression and were able to undergo an R0 resection.[10]

Based on these preliminary data, and the rationale of wanting to initiate best systemic therapy as early as possible, the authors began offering initial, or induction, systemic chemotherapy with 5-FU and oxaliplatin to patients with bulky primaries and/or a large number of lymph nodes. As the comfort level with this approach increased, the authors began to use it more regularly for most patients with clinical stage II or III rectal cancer. Although retrospective, this report was compiled from a computerized search of electronic medical records, thus ensuring that all patients treated with initial chemotherapy during this time frame were included and eliminating recall bias. Although not prospectively selected, based on the initial restriction of this approach to patients with multiple positive nodes and/or bulky disease, the patient population would be anticipated to be overly represented by poor prognosis tumors.

In the authors' experience in this cohort, 100% of patients have experienced objective tumor regressions with initial chemotherapy. R0 resections were achieved in 100% of patients who opted to undergo surgery. The overall pathCR in patients who underwent TME was 27%, with 47% achieving a greater than 90% response. Furthermore, treatment was well tolerated as expected; no grade 4 toxicities occurred. Although initial progression through FOLFOX or CapeOx is rare, it remains a possibility, as demonstrated by Chau et al,[11] wherein 12% of patients did not experience tumor control with induction chemotherapy. For this reason, the authors consider interim evaluation with physical and sigmoidoscopic reexamination by the treating surgeon after approximately 8 weeks of therapy to be an important component of this management approach.

One potential concern with the use of upfront chemotherapy would be the possibility that prior chemotherapy could make it more difficult for patients to tolerate subsequent pelvic radiation therapy. This problem was not encountered, however, and all patients in this report who began treatment with initial chemotherapy were able to complete the combined chemoradiotherapy portion of their treatment without dose-limiting toxicity or treatment interruptions.

This treatment paradigm has several potential advantages. With improvements in surgical techniques and the use of preoperative chemoradiotherapy, the local recurrence rates in rectal cancer have decreased. Thus, most patients with LARC who

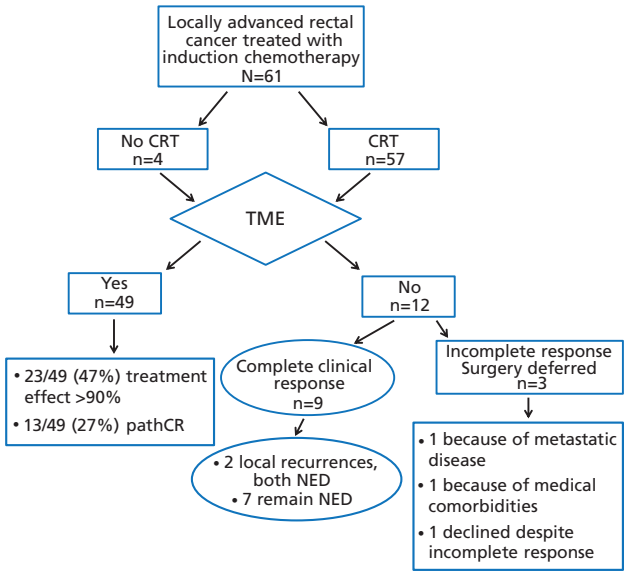

Figure 1 Flow chart summarizing treatment and results. Abbreviations: CRT, chemoradiation; NED, no evidence of disease; pathCR, pathologic complete response; TME, total mesorectal excision.

ultimately succumb to their disease die as a result of distant metastases. Early treatment with best systemic chemotherapy could theoretically allow for a higher likelihood of successful eradication of micrometastatic disease. Although this could not be specifically quantitated in this retrospective analysis, many patients reported rapid relief of symptoms, such as rectal pain or bleeding, often in the first week of receiving systemic chemotherapy. Initial chemotherapy therefore seems to be faster at achieving control of tumor-related symptoms than what has been historically seen with initial chemoradiotherapy. In addition, the delivery of chemotherapy before surgery, when neither radiation nor surgery have impeded blood supply to the tumor and tumor bed, may facilitate optimal delivery of potentially active agents to the primary.

Historically, one of the major shortfalls of adjuvant therapy is that many eligible patients, ranging from 17% to 28% in various trials, either do not start postoperative chemotherapy or initiate treatment after a significant delay (37%–52%).[19–21] The delivery of chemotherapy in a patient with a temporary diverting ostomy is one of the major reasons for treatment delay and toxicities. With the chemotherapy-first approach, patients do not receive any chemotherapy with a temporary ileostomy or colostomy in place. In addition, another tangible benefit is that the time to temporary ostomy reversal is substantially shorter (3 vs 9 months) when no postoperative chemotherapy is planned. A further common concern is that after chemoradiotherapy and surgery, patients cannot complete adjuvant therapy because of high toxicities and poor tolerance.[12,19,21] In this series, all patients were able to complete induction FOLFOX chemotherapy and subsequent chemoradiotherapy without interruption or major toxicities.

Induction chemotherapy also offers the potential benefit of allowing for a longer delay after the completion of radiation before surgery, without the concern for delay of systemic chemotherapy. This is potentially important, because a longer length of time between radiation and surgery has been shown to increase pathologic response rates.[22–25] Several studies have suggested that final pathologic stage is more predictive of long-term outcomes than preclinical stage.[26–31] Furthermore, studies have shown that patients with pathCRs experience excellent outcomes, with overall survival rates ranging from 83% to 96%.[25,26,29,31] A small phase II randomized study did not find a statistically significant rate of increased pathCR, or improvement in rates of failure-free or overall survivals, when comparing neoadjuvant chemotherapy followed by chemoradiotherapy and then surgery and adjuvant chemotherapy versus chemoradiotherapy followed by surgery and adjuvant chemotherapy.[12] However, this study was too small to detect the modest differences likely to be achieved by a simple change in order of administration of the same therapies, and the opportunity to use a longer waiting period before proceeding to surgery was not explored. This trial did not reveal any unexpected toxicities or problems with the use of initial chemotherapy. A definitive phase III trial of this comparison has not and will not be performed because of funding and priority issues.

Recurrence-free and median overall survivals cannot be addressed here, because of the short-interval follow-up of several patients. The numbers are small enough, however, that in the absence of randomized data, such an analysis would be insufficient to be definitive. The authors' experience represents, to their knowledge, the largest series to date of initial chemotherapy and complete delivery of treatment before surgery. The authors believe that these data are sufficiently compelling to be considered as a viable option for LARC. The most recent proposals from the ECOG and National Surgical Adjuvant Breast and Bowel Project have proposed building the next generation of clinical trials for rectal cancer on a platform of chemotherapy before surgery. The order of therapy is not the variable in these protocols; rather, the chemotherapy-first strategy is accepted, and further targeted additions to the initial chemotherapy are the experimental components.

Conclusions

This experience and that of others indicate that upfront chemotherapy is manageable and well tolerated.[11,12] The approach has numerous theoretical advantages over the current chemotherapy-last paradigm. In the absence of large-scale, adequately powered, randomized data, the authors believe that the logic of this paradigm and their preliminary data support the continued use of this approach, particularly for patients with N+ or T4 tumors who are at higher risk for systemic spread. The treatment schema the authors recommend includes in-

terim imaging with MRI and/or endorectal ultrasound to assess for response to chemotherapy.

Given the growing interest in the selective use of nonsurgical, organ-preserving approaches to rectal cancer, the strategy of completing all chemotherapy and chemoradiotherapy before planned surgery offers a favorable paradigm. This paradigm of selective nonsurgical management of LARC will be tested in upcoming clinical trials.

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