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

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Abstract

Background—Standard therapy for locally advanced rectal cancer (LARC) is pre-operative chemo-radiotherapy (CRT) and post-operative chemotherapy. We began offering FOLFOX (5FU, leucovorin and oxaliplatin) as initial treatment for patients with high-risk LARC to target micrometastases, while treating the primary tumor.

Purpose—To report safety and efficacy of initial FOLFOX before CRT on tumor downsizing and pathologic complete response (pathCR) in LARC.

Patients and Methods—IRB waiver was obtained to review records of stage II/III rectal cancer patients (pts) treated at MSKCC between 2007 and 2012. Of approximately 300 LARC pts treated with CRT, 61 received FOLFOX as initial therapy.

Results—Of the 61 pts, 57 received induction FOLFOX (median 7 cycles) then CRT, 4 pts had an excellent response, declined CRT, and had total mesorectal excision. Twelve pts did not undergo TME; 9 had a complete clinical response (CCR); 1 declined despite persistent tumor, 1 due to comorbidities, 1 developed metastatic disease. 22/61 patients (36%) had either pathCR (n=13) or CCR (n=9). Of the 49 pts who underwent TME, all had R0 resections, 23 (47%) had tumor response >90%, including 13 (27%) pathCR. 28 pts received all 8 cycles of FOLFOX, 8 had pathCR (29%) and 3 CCR (11%). There were no serious adverse events requiring delay in treatment during FOLFOX or CRT.

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Conclusion—FOLFOX and CRT before planned TME results in tumor regression, a high rate of delivery of planned therapy, substantial rate of pathCRs and offers a good platform for potential non-operative management in select patients.

Keywords

Rectal cancer; FOLFOX; pathologic complete response; induction chemotherapy

Introduction

Modern therapy for locally advanced rectal cancer, with the combination of pre-operative chemo-radiotherapy and improved surgical techniques has led to significant improvements in local control for this disease. Distant recurrence rates now exceed the rates of local recurrence.^{1,2} The current standard management for Stage II (T3/T4N0) and Stage III (Tany, N1/N2) rectal cancer is neoadjuvant chemo-radiotherapy, followed by surgery and the 4 months of adjuvant systemic chemotherapy is given at the end.^{1,23} While neoadjuvant chemo-radiotherapy has been shown to decrease the incidence of local recurrence, the risk of distant metastases and overall survival has not been shown to be impacted by radiation therapy.^{5,6}

Advances in systemic chemotherapy with the addition of oxaliplatin to 5-fluorouracil have resulted in improved survival in patients with metastatic colorectal cancer as well as for patients with Stage III colon cancer treated with adjuvant FOLFOX (5-FU, leucovorin, oxaliplatin) chemotherapy.^{7–10} Response rates for patients with metastatic colorectal cancer treated with modern chemotherapy regimens such as FOLFOX have routinely exceeded 40–50%^{7,8} Furthermore, there are data to suggest that the primary tumor may in fact be more sensitive to systemic chemotherapy than metastases.^{11,12}

Thus, with the improvements in systemic therapy, there are now a number of theoretical considerations that favor the use of up front chemotherapy in LARC patients. Of primary importance in the high-risk rectal cancer population, the current rectal cancer treatment paradigms do not deliver optimal combination systemic chemotherapy for approximately 3 to 4 months from initiation of neoadjuvant chemoradiotherapy, and this delay is theoretically disadvantageous in that it allows a window for growth of distant micrometastases which may already exist. Best systemic therapy early on offers the potential to optimally treat micrometastatic disease. Initial chemotherapy also permits delivery of chemotherapy agents directly to the primary tumor while it has a fully intact vasculature, undisturbed by radiation or surgery. Finally, there is the practical consideration that completion of all planned treatment prior to surgery allows for those patients requiring a temporary diverting ostomy to avoid the challenges of chemotherapy with an ostomy. It also decreases the duration of temporary ostomies (as little as eight weeks) than if post operative chemotherapy is planned.

The above-cited considerations, plus favorable data from preliminary reports exploring this strategy,^{12–14} provides a solid rationale for shifting systemic treatment earlier into the treatment paradigm. Based on these data, we began altering the sequence of treatment for most patients with locally advanced rectal cancer at MSKCC, offering patients initial chemotherapy (ICT) with FOLFOX followed by chemoradiotherapy and then TME. In this

manuscript we report the initial efficacy results of our experience with this approach, as well as the associated toxicities.

Patients and Methods

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

Patients received standard mFOLFOX6 chemotherapy administered every two weeks.⁸ Two patients refused mediports; one received CapeOx (capecitabine plus oxaliplatin) and another patient received the FLOX regimen with weekly bolus 5FU and oxaliplatin every 2 weeks.^{15,16}

Monitoring During Induction Chemotherapy

All of the patients were assessed with interval imaging either with MRI or endorectal ultrasound for response or progression. The majority were reimaged after approximately 4–6 cycles.

Chemo-radiotherapy

Radiation therapy was administered approximately 2–3 weeks after completion of chemotherapy with standard fractionation with either concurrent infusional 5FU (225mg/m² continuous throughout radiation or capecitabine 825 mg/m² twice daily, Monday–Friday during RT).

All patients underwent computed tomography (CT) simulation in the prone position. The gross tumor volume (GTV) consisted of the primary tumor and enlarged regional lymph and the clinical target volume (CTV) consisted of the GTV, rectum, and lymph node regions including mesorectum, pre-sacral nodes, internal iliac nodes, and the superior rectal nodes. Patients underwent either 3D conformal (3DCRT) or intensity modulated radiotherapy (IMRT) treatment planning with the in-house planning software. 3DCRT plans consisted of three or four orthogonal beams for the pelvic fields and two lateral beams and one posterior-anterior beam for the boost fields. PTV was treated to 45 Gy in 1.8 Gy fractions followed by a 5.4 Gy boost to PTV-boost to a total dose of 5040cGy. IMRT plans consisted of 5–7 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 6–8 weeks after completion of chemoradiation at MSK by one of 6 colorectal surgeons specialized in total mesorectal excision for rectal cancer. The choice of the surgical procedure abdominoperineal resection (APR) or low anterior resection (LAR) was at the surgeons discretion. Complete clinical response was defined as no visible tumor on ERUS or imaging with CT or pelvic MRI.

Pathologic Assessments

The pathologic specimens after TME were evaluated using standard pathological guidelines. In case of residual macroscopic tumor, standard pathological examination was carried out with three to five 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.¹⁷ Pathological complete response (pCR) was defined as the complete disappearance of all tumor cells.

Results

Patient Characteristics

Of approximately 300 rectal patients treated at MSKCC and its regional sites with CMT between 2007 and 2012, 61 received some or all of their planned chemotherapy as the initial treatment of their LARC. The median age was 52. Twenty-eight patients were female and 33 male. 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.

ICT administration and toxicities

Of the 61 patients, 28 received a full 8 cycle course of initial chemotherapy with 5FU and oxaliplatin. The median number of cycles was 7 (range was 2–12). Notably, since this was not a prospective study, there was not a pre-specified treatment plan. Therefore, some patients received their FOLFOX treatment at split times, i.e., before and after surgery. All patients, however, including those that declined surgery or radiation, received at least 8 cycles of FOLFOX. More recently our intent has been to deliver the full course of planned chemotherapy up front, without interruption. Of the 42 patients treated in calendar years 2011 and 2012, 30 received all of their FOLFOX prior to CRT.

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. There were no grade 4 toxicities and no serious adverse events requiring a break in treatment. (See Table 2).

Chemoradiotherapy administration and toxicities

Of the 61 patients treated with initial chemotherapy, 4 patients who achieved 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, there were no grade 4 toxicities and no serious adverse events requiring a treatment break. Thus, all patients were able to complete CRT 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%). (See Table 3).

Surgery and Surgical Morbidity

Of the 61 patients, 12 did not undergo surgery. Of these, 9 had a complete clinical response and elected to be managed non-operatively; 1 refused recommended surgery despite incomplete tumor regression, and 1 had surgery deferred due to 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, two had pelvic abscesses requiring drainage and one had an anastomotic leak requiring reoperation. There were no postoperative mortalities. 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 to 179).

Pathologic and Clinical Response to Therapy

Of the 61 patients, 22 (36%) had either a pathCR (13) or a complete clinical response (9), the latter of which were treated with non-operative management. Of the 49 patients who underwent resection, 23 (47%) had tumor response >90%, including 13 (27%) with pathCR. Of those 49 patients, 46 patients had node positive disease (u or m TxN1/2), and 30 (65%) were down staged to ypN0. Table 4 lists the clinical and pathologic staging.

The median follow up from the start of induction chemotherapy of all patients is 17.8 months (range 69 months to 10.7 months). Five of the 61 patients have developed recurrent metastatic disease; one underwent resection of an isolated lung metastasis while three remain alive with unresectable metastatic disease. The fifth patient developed a second primary colon cancer with liver metastases. Of the 28 patients who received all 8 cycles of initial FOLFOX, 8 achieved a pathCR (29%) and an additional 3 achieved a complete clinical response (11%) and have been managed non-operatively. Of note, none of the 61 patients treated had progression of the primary tumor while receiving initial chemotherapy or subsequent chemo-radiotherapy. All of the patients had clinical regression in the primary as observed by proctoscopic examination and/or MRI. Of the 49 patients who underwent TME, all but 2 achieved pathologic down-staging. The two who did not change staging remained at T3N2, but did have clinical regression based on ERUS and 20–40% treatment effect in the tumor. Of note, both of these patients had tumors with factors associated with a negative prognosis for response; one of these patients had Lynch syndrome and the second had a signet ring cell adenocarcinoma.

Of 12 patients who did not undergo TME, 9 had a complete or near-complete clinical response and were followed closely. One patient recurred locally 6 months after completion of therapy and underwent transanal resection of a ypT1Nx adenocarcinoma. One patient underwent resection 7 months post completion of therapy for clinical concern of 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 months– 10.7 months). The treatment schema and results are summarized in Figure 1.

Discussion

The concept of neoadjuvant initial chemotherapy prior to radiotherapy in locally advanced rectal cancer was first explored in a clinical trial by Chau et al which demonstrated an 88% objective tumor control rate with neoadjuvant capecitabine/oxaliplatin.^{13,18} In a single institution trial at our center that started in March, 2007, 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 had tumor regression and were able to undergo an R0 resection.¹²

Based on these preliminary data, as well as the rationale of wanting to initiate best systemic therapy as early as possible, we began offering initial, or induction, systemic chemotherapy with 5FU and oxaliplatin for patients with bulky primaries and/or a large number of lymph nodes. As our comfort level with this approach increased, we 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 insuring that all patients treated during this timeframe with initial chemotherapy are included, and so eliminating recall bias on this issue. Although not prospectively selected, based on our initial restriction of this approach to patients with multiple positive nodes and /or bulky disease, our patient population would be anticipated to be overly represented by poor prognosis tumors.

In our experience in this cohort, 100% of patients have achieved objective tumor regressions with initial chemotherapy. R0 resections were achieved in 100% of patients who opted to undergo surgery. The overall complete pathologic response in patients who underwent TME was 29%, with 47% achieving greater than 90% response. Furthermore, treatment was well tolerated as expected; there were no grade 4 toxicities. Although initial progression through FOLFOX or CapeOx is rare, it remains a possibility, as has been demonstrated by Chau et al wherein 12% of patients did not achieve tumor control with induction chemotherapy.¹³ For this reason we regard interim evaluation with physical and sigmoidoscopic reexamination by the treating surgeon after approximately 8 weeks of therapy as an important component of this management approach.

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

As noted previously, there are several potential advantages to this treatment paradigm. With improvements in surgical techniques and the use of preoperative chemo-radiotherapy, the

local recurrence rates in rectal cancer have decreased. Thus, the overwhelming majority of patients with locally advanced rectal cancer who 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 we could not specifically quantitate this in our 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 appears in our estimation to be faster at achieving control of tumor-related symptoms than what we have seen with initial chemo-radiotherapy historically. 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 start to receive the doses 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 to the patients is that the time to temporary ostomy reversal is substantially shorter (3 months vs 9 months) when no post-operative chemotherapy is planned. A further common concern is that following chemoradiotherapy and surgery patients cannot complete adjuvant therapy due to high toxicities and poor tolerance.^{14,19,21} In our series, thus far, all patients have been able to complete induction FOLFOX chemotherapy and subsequently chemoradiotherapy without interruption or major toxicities.

Induction chemotherapy also adds 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 demonstrated that patients with complete pathologic responses achieve excellent outcomes with overall survival rates ranging from 83–96%.^{25,26,29,31} A small phase II randomized study did not find a statistically significant rate of increased pathological CR, or improvement in rates of failure free survival or overall survival comparing neoadjuvant chemotherapy followed by CRT then surgery and adjuvant chemotherapy to CRT followed by surgery and adjuvant chemotherapy.¹⁴ However, this study was far 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 utilize 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 done due to funding and priority issues.

In this current report, we are unable to address recurrence free and median overall survival due to the short interval follow up of a number of patients. The numbers are small enough, however, that in the absence of randomized data, such an analysis would be insufficient to be

definitive. Our experience represents, to our knowledge the largest series to date of initial chemotherapy and complete delivery of treatment prior to surgery. We believe that this data is sufficiently compelling to be considered as a viable option for locally advanced rectal cancer. The most recent proposals from ECOG and NSABP 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.

In conclusion, experience strongly indicates that chemotherapy up-front is manageable and well tolerated. The approach has numerous theoretical advantages over the current chemotherapy-last paradigm. In the absence of large scale, adequately powered, randomized data, we feel that the logic of this paradigm and our preliminary data support the continued use of this approach, particularly for those patients with N+ or T4 tumors who are at higher risk for systemic spread. Our recommended treatment schema includes interim imaging with MRI and or endorectal ultrasound to assess for response to chemotherapy.

With growing interest in selective use of non-surgical, organ preservation approaches to rectal cancer, the strategy of completing all chemotherapy and chemo-radiotherapy before planned surgery offers a favorable paradigm. We will be testing this paradigm of selective non-surgical management of locally advanced rectal cancer in upcoming clinical trials.

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Figure 1.
Flow Chart summarizing treatment and results

Table 1

Patient Characteristics

Baseline Characteristics	Number of Patients Total = 61	%
Sex	--	--
Male	33	54%
Female	28	46%
Age, years	--	--
Average	52	
Range	25–82	
Performance Status	--	--
(ECOG)	--	--
0	42	69%
1	18	31%
Initial Diagnosis Stage*		
T3N0	7	8%
T3N1	24	43%
T3N2	23	39%
T4N0	1	2%
T4N1	4	6%
T4N2	2	4%

Table 2

Chemotherapy Toxicities

Toxicity	Grade 1	Grade 2	Grade 3/4
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

Table 3

Chemoradiotherapy Toxicities

Toxicity	Grade 1	Grade 2	Grade 3/4
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

Table 4

Clinical and pathologic staging

Initial Staging N=49	Pathologic Staging N=49									
	ypT0N0	ypT1sN0	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			