

Scientific Article

Phase 1 Study of Neoadjuvant Short-Course Radiation Therapy Concurrent With Infusional 5-Fluorouracil for the Treatment of Locally Advanced Rectal Cancer



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Abstract

Purpose: To assess the safety and feasibility of neoadjuvant short-course radiation therapy (RT) concurrent with continuous infusion 5-fluorouracil (5-FU) for the treatment of locally advanced rectal cancer.

Methods and Materials: Patients with cT3-4 or N + rectal adenocarcinoma based on ultrasound or magnetic resonance imaging were prospectively enrolled in this study. Study treatment consisted of continuous infusion 5-FU combined with short-course RT (5 Gy x 5 fractions) followed by 4 cycles of mFOLFOX, total mesorectal excision (TME), and 6 cycles of adjuvant mFOLFOX. To mitigate the potential added toxicity from concurrent 5-FU, intensity modulated RT was used. Using the continual reassessment method, the dose of 5-FU was escalated from 100 to a maximum-tolerated dose of 200 mg/m²/d.

Results: Fourteen patients were accrued. All patients completed continuous infusion 5-FU and short-course RT and the 5-FU dose was safely escalated to 200 mg/m²/d with no dose-limiting toxicity. Thirteen patients received the neoadjuvant mFOLFOX, and only 1 patient went straight to surgery after chemoradiation. Clinical response was 21% complete, 63% partial, 14% stable disease, and no patients had progression. Three patients with cCR had negative biopsies and did not have TME. Pathologic response was 64% partial response and 14% stable disease. No patients had pathologic progression. The most common grade 3 and 4 toxicities were cytopenias. The most common grade 1 and 2 toxicities were cytopenia, fatigue, diarrhea, and nausea.

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Conclusions: Our findings suggest that concurrent chemotherapy with neoadjuvant short-course RT is feasible and can be safely given with concurrent continuous infusion 5-FU. This works adds to the growing evidence that short-course RT is not only equivalent to long-course RT, but also may provide additional benefits, such as allowing for a transition to full dose systemic therapy in the neoadjuvant setting, selective organ preservation in complete responders, and providing a more convenient and cost-effective way of delivering pelvic RT.

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Introduction

Preoperative chemoradiotherapy is standard of care for patients in the United States with locally advanced rectal cancer. Historically, 5-fluorouracil (5-FU) has most commonly been used concomitantly with external beam radiation as a radiosensitizer. Two large randomized clinical trials have demonstrated improved local control and pathologic complete response (pCR) rates when fluorouracil-based chemotherapy is given concurrently with standard fractionated pelvic radiation therapy (RT; ie, long-course chemoradiotherapy) in the neoadjuvant setting.^{1,2} The results of the German Rectal Cancer Trial comparing preoperative versus postoperative long-course chemoradiation demonstrated that the toxicity of chemoradiotherapy is reduced and local control is improved with a neoadjuvant approach, thus representing the current prevailing treatment paradigm.³

Standard or long-course chemoradiotherapy typically consists of 5.5 weeks of RT (50.4 Gy in 28 daily fractions). However, there is a large and growing body of literature that supports the use of shorter courses of radiation (hypofractionated or short-course RT) that dates back to the original Swedish and Dutch rectal cancer trials that helped to establish RT as a cornerstone in the management of rectal cancer.^{4,5} Traditionally, short-course RT has been delivered in 5 fractions over 5 consecutive days with patients proceeding to surgical resection 1 week after the last fraction.

Two randomized trials have been published comparing the 2 treatment philosophies, one from the Trans-Tasman Radiation Oncology Group (TROG) and another from Poland.^{6,7} These trials showed no difference in local control, disease-free survival, or overall survival between long-course chemoradiation and short-course RT. Furthermore, there were no significant differences in late toxicity between the 2 regimens, and in fact, short-course RT resulted in less acute toxicity. As a result of these findings, European Society for Medical Oncology consensus guidelines currently incorporate short-course neoadjuvant RT as a reasonable approach for all but the

most advanced rectal cancers where they recommend either short course RT followed by neoadjuvant systemic therapy or long course RT to allow more time for down-staging both during and after treatment.⁸ Indeed, the traditional short-course RT paradigm calls for surgery to be performed 1 week after RT, compared with the 4 to 6 week interval to surgery that has become standard for long-course chemoradiotherapy. This has led to criticism of the short-course RT paradigm, as it potentially precludes a sphincter-preserving resection for patients who may otherwise be spared a permanent colostomy if significant tumor down-staging occurs after long-course chemoradiotherapy. Randomized evidence does not, however, support this critique, as both the TROG and Polish randomized studies showed similar rates of sphincter preservation between long-course chemoradiation and short-course RT alone. Nevertheless, modified short-course RT protocols that incorporate a delay between RT and surgery seek to address this concern that remains prevalent among the US oncology community. The Stockholm III trial was a 3-arm trial that compared short-course RT with the standard 1-week delay to surgery, short-course RT with a 4- to 6-week delay to surgery, and long-course chemoradiation with a 4- to 6-week delay to surgery. The results show similar outcomes between the groups, but delaying the surgery after short-course RT decreased the rates of high-grade toxicity and allowed for an expedited treatment program.⁹ This finding was confirmed in a recent meta-analysis of 1244 patients.¹⁰ Together, these data suggest that if short-course RT is combined with a delayed time interval before proceeding to surgery, rates of clinical tumor down-staging and sphincter preservation should be comparable to that of standard long-course chemoradiation.

An additional criticism of the neoadjuvant short-course RT paradigm is that it inherently delays systemically active chemotherapy until after recovery from surgery. The rate of distant metastasis in locally advanced rectal cancer is $\approx 30\%$, and adjuvant chemotherapy is an essential component of treatment, which has been shown

to decrease the risk of disease recurrence by 25% in a Cochrane meta-analysis.¹¹ However, for various reasons, ≈20% to 30% of patients do not receive adjuvant chemotherapy as intended.^{2,12} As standard long-course chemoradiation incorporates systemic chemotherapy upfront, this poses a theoretical timing and compliance advantage over the short-course RT paradigm as it currently exists.

To date, there has been hesitancy to combine short-course RT with chemotherapy or novel radiosensitizers owing to the theoretical concern for unacceptable toxicity.¹³ However, the toxicity results from the Polish and TROG randomized trials suggest that there is room for treatment intensification with short-course RT. We therefore proposed to administer 5-FU concurrently with short-course RT in the hopes of achieving similar magnitudes of improved local control as previously demonstrated with the addition of 5-FU to long-course RT.

To mitigate the potential added toxicity from 5-FU given with short-course RT, we used intensity modulated RT (IMRT). IMRT has previously been demonstrated to be effective in reducing small bowel dose and resultant gastrointestinal toxicity in patients with other pelvic malignancies¹⁴⁻¹⁶ and research into the potential benefits of IMRT in the treatment of rectal cancer have only recently been undertaken.^{17,18}

The primary objective of this trial was to assess the safety and feasibility of 5-FU given concurrently with 5 Gy x 5 fractions IMRT. The secondary aims were to assess the response rate after delayed surgery with mFOLFOX given in the interim.

Methods and Materials

Patient eligibility

Patients eligible for study entry were required to have pathologically proven adenocarcinoma, determined to be clinically staged (American Joint Committee on Cancer 7th ed) T3-4 N0 M0 or T any N1-2 M0 and deemed a candidate for curative resection by the surgical oncologist performing the operation. The minimum age for eligibility was 18 years, and performance status on the Eastern Cooperative Oncology Group scale was 0 or 1. Patients were required to have adequate renal, hepatic, and hematologic organ function.

Pretreatment staging included a computed tomographic (CT) scan of the chest, abdomen, and pelvis, a complete colonoscopy, and either a transrectal endoscopic ultrasound (EUS) or pelvic magnetic resonance imaging (MRI) for T staging. After neoadjuvant therapy and before surgery, chest, abdomen, and pelvis imaging was repeated to ensure no metastatic progression.

Under institutional review board approval and in accordance with an assurance filed with and approved by

Table 1 IMRT dose constraints

Structure	Dose constraint	Goal percentage	Goal volume
PTV	≥98%	≥93%	
	≤10%	≥105%	
	≤5%	≤110%	
	0%	≥115%	
Intensity modulated	19.5 Gy		180 mL
	22.2 Gy		100 mL
	25 Gy		65 mL
	27.8 Gy		0 mL
Femoral heads	22.2 Gy	40%	
	25 Gy	25%	
	27.8 Gy	0%	
Bladder	22.2 Gy	40%	
	25 Gy	15%	
	27.8 Gy	0%	

PTV, planning target volume.

the Department of Health and Human Services, informed consent was obtained from each participant.

Treatment

Short-course RT

Short-course RT was given in 5 fractions of 5 Gy to a total dose of 25 Gy over 5 consecutive days. Patients had a CT simulation for radiation planning in either a prone or a supine position with a full bladder for both planning and daily treatment. The gross tumor volume included the primary tumor and any involved pelvic lymph nodes based on staging imaging studies and clinical examination. The clinical target volume included the standard at-risk lymph node basins for rectal cancer, the internal iliac, presacral and perirectal regions, and was defined based on the RTOG contouring atlas. A 5-mm expansion was added to the clinical target volume for the final planning target volume.

IMRT plans were generated with ≥6 MV photons, with planning goals including ≥98% of the planning target volume receiving ≥93% of the prescribed dose, with limitations on hot spots such as ≤10% and ≤5% receiving ≤105% and ≤110% of the prescribed dose, respectively. The constraints on the organs at risk were scaled from the RTOG 0822 rectal cancer protocol and included volumetric and maximum dose constraints on the small bowel, bladder, and femoral heads (Table 1, Fig 1). Daily image guidance was used with orthogonal kV imaging or cone beam CT with an alignment priority of the pelvic bony anatomy.

Dose-escalated concurrent 5-FU

The 3 doses levels of 5-FU were 100, 150, and 200 mg/m²/d. 5-FU was given by continuous infusion for 96 hours via PORT-a-Cath starting on the morning of

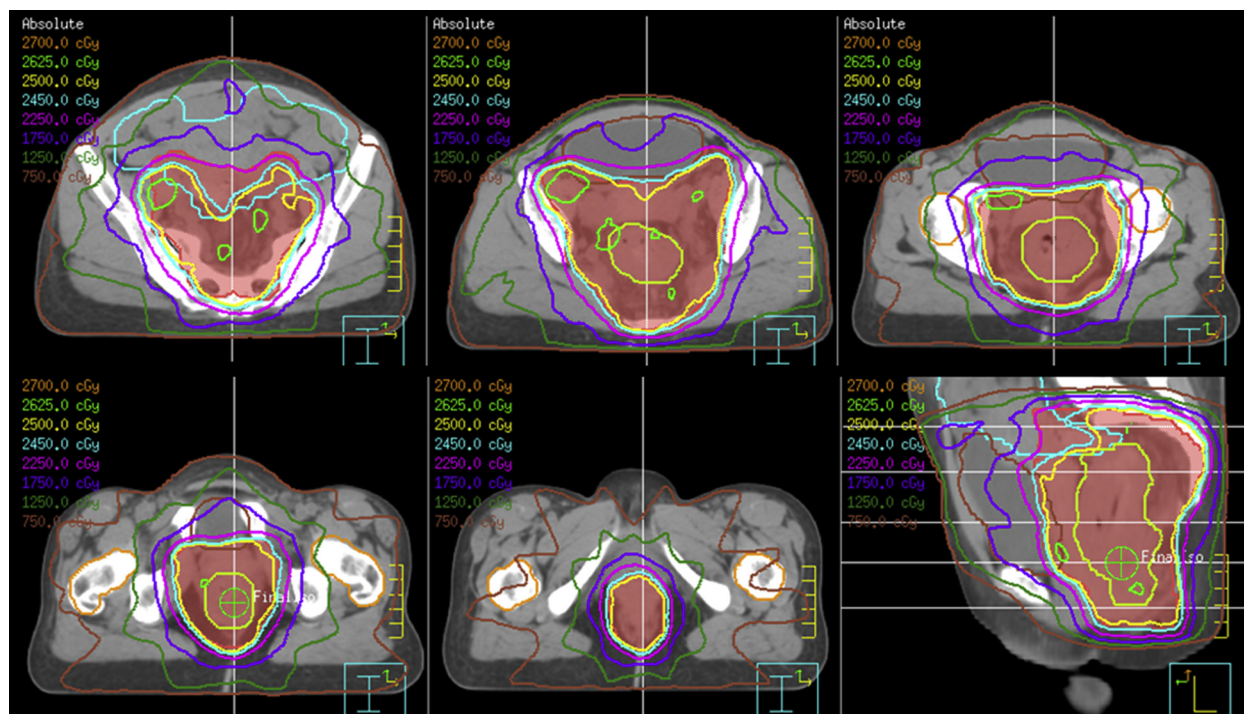


Figure 1 Example of an intensity modulated radiation therapy treatment plan with representative axial and sagittal images.

radiation. On the final day of chemoradiation, the pump was disconnected in the oncology clinic.

mFOLFOX

5-FU, leucovorin, and oxaliplatin (mFOLFOX6) was given 2 weeks after concurrent 5-FU and IMRT for a total of 4 cycles, with each cycle being 14 days. The 5-FU was given as a continuous infusion over 46 hours at a dose of 2400 mg/m², the oxaliplatin was 85 mg/m² IV over 2 hours, and the leucovorin was 350 mg/m² IV concurrently with the oxaliplatin.

Six cycles (each cycle being 14 days) of mFOLFOX6 was also administered postoperatively to patients who had a complete resection of rectal cancer or immediately after chemoradiation to patients who had a complete response (CR) after chemoradiation and preoperative chemotherapy and declined surgery. Postoperative chemotherapy began no earlier than 4 weeks and no later than 8 weeks after surgical resection.

Response and toxicity assessment

Toxicities were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Dose-limiting toxicity (DLT) was defined as any of the following occurring during chemoradiation or within 21 days from the completion of chemoradiation and reported as probably or definitely related to treatment: (1) grade 4 nonhematologic toxicity, (2) grade 4 febrile neutropenia, (3) grade 4

thrombocytopenia or neutropenia toxicity lasting >7 days, (4) grade 3 nonhematologic toxicity, preventing treatment for >3 days, or (4) elevation of ALT or AST >10 x upper limit of normal for >7 days. The dose-finding portion of this phase 1 study was for the 5-FU administered during the short-course RT. Therefore, DLTs were defined during this period. The 21-day period was selected because the toxicity from short-course RT is commonly seen 1 to 2 weeks after treatment with a rapid resolution afterward. Some toxicity from the first cycle of mFOLFOX may be captured, but given the timeframe it is unlikely to be a DLT.

Clinical response assessment was done with CT or magnetic resonance imaging within 14 days before surgery and based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria. pCR was defined as no residual tumor in the surgical specimen.

Statistical considerations

To ensure maximal accrual at the MTD, a Bayesian Continual Reassessment method was implemented for this trial.^{19,20} The initial cohort size at each dose level was 2 patients. The DLT probability is modeled using a one-parameter logistic curve, assuming 10%, 20%, and 30% probability at the 3 planned dose levels. The parameter of the logistic curve was updated using a Gamma distribution, using Bayesian updating of the likelihood of the current DLT data. The study starts at the lowest dose level. After 2 patients are recruited, the dose

Table 2 Baseline patient and disease characteristics

Total no. of patients treated: 14	
Sex (no. of patients)	
Female	8 (57.1%)
Male	6 (42.9%)
Race (no. of patients)	
Black or African American	5 (35.7%)
White	9 (64.3%)
Unknown	—
Age (y)	
Median	58
Range	28-77
Staging examination	
Endoscopic ultrasound	8 (57.1%)
Pelvic MRI	8 (57.1%)
Both	2 (14.3%)
T staging	
T3	13 (92.9%)
T4	1 (7.1%)
TNM staging	
N0	3 (21.4%)
N1	7 (50%)
N2	4 (28.6%)
Distance from anal verge	
>10 cm	2 (14.3%)
5-10 cm	6 (42.9%)
<5 cm	6 (42.9%)

toxicity curve is updated and dose escalation to the next level is approved only if the posterior probability of DLT at the next level is <30%. Otherwise, only the maximum dose with posterior DLT probability <30% is recommended for accrual. Once escalation is not possible, patients are accrued at the current level until 8 evaluable patients are treated at the MTD.

Results

Patients

Based on the statistical model, 12 patients were planned to be enrolled if no DLT occurred. However, because some patients were not evaluable for the primary endpoint, 14 patients were accrued between May 2015 and February 2017 with a median age of 58 (range 28-77 years). The first 7 patients enrolled had an EUS for tumor staging and the second 7 had pelvic MR imaging. In our study we saw a change from the use of EUS to MRI for the staging of our rectal cancer patients. Although there is currently no consensus on a preferred imaging technique for preoperative staging of rectal cancer, MRI has certainly taken over at our institution given its high interrater reliability, accurate nodal staging, and improved patient comfort.

Table 3 Acute toxicities by dose level

Dose level	N (%)	Grade	Grade	Grade	Grade
		1	2	3	4
		N (%)	N (%)	N (%)	N (%)
1 (100 mg/m ² /d)	2 (100)	0 (0)	1 (50)	1 (50)	0 (0)
2 (150 mg/m ² /d)	2 (100)	1 (50)	0 (0)	1 (7)	0 (0)
3 (200 mg/m ² /d)	10 (100)	0 (0)	3 (30)	5 (50)	2 (20)

The tumors were well distributed along the length of the rectum, with about 43% within 5 cm of the anal verge (Table 2).

Safety and tolerability

All 14 patients completed the short-course RT with 5-FU within the specified 5-day period. The 5-FU was safely escalated from 100 mg/m²/d (N = 2) to 150 mg/m²/d (N = 2) to 200 mg/m²/d (N = 10) with no DLT. There were 2 patients in the highest dose level with grade 4 neutropenia, but given that it lasted <7 days was not counted as a DLT (Tables 3 and 4). Overall, this regimen was fairly well tolerated. The most common grade 3 and 4 toxicities were decreased neutrophil count (21.4%) and decreased lymphocyte count (21.4%; Table 4). The most common grade 1 and 2 toxicities included diarrhea (71.4%) fatigue (71.4%), decreased lymphocyte count (64.3%), nausea (57.1%), anemia (57.1%), decreased platelet count (50%), decreased white blood cell count (50%), and rectal pain (42.9%). Proctitis was not common and only reported in 3 patients (21.4%), 2 were grade 2 (14.3%) and 1 grade 1 (7.1%). Thirteen of the patients received preoperative mFOLFOX. One patient went straight to surgery after short-course RT and had a radiographic microperforation that was possibly related to study treatment but felt more likely to be related to disease; the patient was not considered a good candidate for further cytotoxic therapy.

Only 9 of the 14 patients completed all 4 cycles of neoadjuvant therapy. In addition to the one patient with a microperforation, there was one patient who had a single cycle of mFOLFOX preoperatively who was expedited to surgery for persistent nausea and vomiting likely to be related to tumor burden (T3 tumor, 7 cm in length) and 2 patients who omitted cycle 4 owing to cytopenias.

Ten of 14 (71.4%) completed the postoperative FOLFOX (Table 5). Of those who did not complete the adjuvant chemotherapy, 2 patients did not complete adjuvant therapy owing to poor wound healing, one patient with a positive surgical margin had a change in management strategy, and the fourth patient received no additional treatment after achieving a clinical CR with the short-course RT and 4 cycles of mFOLFOX.

Table 4 Grade 3 and 4 adverse events possibly, probably, or definitely related to study treatment*

Toxicity	N (%)	Grade	
		Grade 3 N (%) [†]	Grade 4 N (%) [‡]
Blood and lymphatic system			
Febrile neutropenia	1 (7.1)	1 (7.1)	
Gastrointestinal			
Abdominal pain	2 (14.3)	2 (14.3)	
Colitis	1 (7.1)	1 (7.1)	
Colonic obstruction	1 (7.1)	1 (7.1)	
Constipation	1 (7.1)	1 (7.1)	
Nausea	1 (7.1)	1 (7.1)	
Rectal perforation	1 (7.1)	1 (7.1)	
General disorders			
Fatigue	1 (7.1)	1 (7.1)	
Fever	1 (7.1)	1 (7.1)	
Investigations			
Lymphocyte count decreased	3 (21.4)	3 (21.4)	
Neutrophil count decreased	3 (21.4)	1 (7.1)	2 (14.3) [‡]
White blood cell decreased	2 (14.3)	2 (14.3)	
Metabolism and nutrition			
Dehydration	2 (14.3)	2 (14.3)	
Hypocalcemia	1 (7.1)	1 (7.1)	
Hypokalemia	1 (7.1)	1 (7.1)	
Hyponatremia	1 (7.1)	1 (7.1)	
Hypophosphatemia	1 (7.1)	1 (7.1)	
Renal and urinary			
Acute kidney injury	1 (7.1)	1 (7.1)	
Vascular			
Hypotension	1 (7.1)	1 (7.1)	
Thromboembolic event	1 (7.1)	1 (7.1)	

* When a patient had multiple records for the same toxicity, the one with the highest grade was counted.

[†] The denominator was 14 (total no. of patients).

[‡] Resolved within 1 and 4 days.

Table 5 Receipt of treatment

Treatment type	Patients completed N (%)	Target interval	Cycles N (%)	
			Median	Range
Short-course RT + 5-FU	14 (100)	5 days		
Preoperative FOLFOX	9 (64.3)	6 weeks	4	0-6
Postoperative FOLFOX	10 (71.4)	8 weeks	6	0-12

had TMEs had sphincter-preserving operations (Table 6).

At a median follow-up of 12 months, the local-regional recurrence rate was 0.254 and the disease-free survival rate was 0.746.

Discussion

Short-course RT is an accepted alternative to long-course chemoradiation for the neoadjuvant treatment of locally advanced rectal cancer⁶; however, in the United States, the short-course approach is not commonly used.²¹ Some of the factors related to the neglect of short-course RT include no use of concurrent chemotherapy, less chance of tumor down-staging with the traditional short interval between RT and surgery, and an increased risk of late toxicities.²¹ In this phase 1 study, we have shown that fluorouracil-based chemotherapy can be safely given concurrently with short-course RT, the interval between short-course RT and surgery can be prolonged with excellent rates of down-staging, and toxicities are manageable. In fact, the short-course regimen has attractive benefits, including patient convenience and lower costs. Even when using IMRT, the cost of short-course RT compared with long-course 3D-CRT is substantially less, and this may become more important as payers move toward bundled-care payments.²²

In our study, we observed a clinical CR rate of 21.4%, with 3 patients having a durable clinical response now almost 2 years out from study treatment. These patients had low-lying rectal tumors and were able to avoid disfiguring surgical resection. However, because these patients did not have surgery, the pCR rate could not be reported. Of the other patients, 64.3% had a pPR and 14.3% had stable disease at the time of surgery. Assuming our patients with a CR, now with durable responses, would have had a pCR, our results compare favorably with other neoadjuvant approaches. Myerson et al used a similar study design with short-course IMRT followed by 4 cycles of FOLFOX and reported a pCR rate of 25%.²³

To date, there has been hesitancy to combine short-course RT with chemotherapy or novel

Treatment response

Three of the 14 patients (21.4%) had a clinical CR by CT/MR imaging and clinical examination. All 3 of these patients had tumors within 5 cm of the anal verge and none of them proceeded with TME. At a median follow-up of 21 months (range 19-32 months), none of these patients had a recurrence or had any surgery for their rectal cancer. Of the other patients, 9 (63.4%) had a clinical partial response (PR), 2 (14.3%) had stable disease, and no one had disease progression.

Of the 10 patients who had TMEs, 9 (90%) had an R0 resection, 9 (63.4%) had a pathologic PR, 2 (14.3%) had stable disease, and no one had pathologic disease progression. In total, 12 patients (85.7%) were able to preserve their sphincter, and 9 of the 10 who

Table 6 Response to preoperative treatment

Response N (%) [*]	Complete response	Partial response	Stable disease	Disease progression	R0	Anal sphincter preservation
Clinical response	3 (21.4)	9 (63.4)	2 (14.3)	0 (0)	9 out of 10 patients who had surgery	12 (85.7)
Pathologic response [*]	0 (0)	9 (63.4)	2 (14.3)	0 (0)		

^{*} Pathologic response data not available for 3 patients.

radiosensitizers owing to the theoretical concern for unacceptable toxicity. When our protocol was developed, there was no data on concurrent chemotherapy with short-course RT. However, a South Korean group developed KROG-10-01, which is similar in premise to our study using preoperative short-course concurrent chemoradiation with delayed surgery. There were 73 patients in KROG-10-01 who received 25 Gy with tomotherapy and 400 mg/m²/d 5-FU and 20 mg/m²/d leucovorin delivered by intravenous bolus.²⁴ Unfortunately, this study had low rates of pCR (1.4%) and unacceptable rates of toxicity. Grade 3 or higher toxicities were recorded in 38% of patients, with the most common nonhematologic toxicity being abdominopelvic pain. The toxicity in our study is much lower than that reported in the KROG 10-01 study and may be explained by the dose and delivery mechanism of the concurrent 5-FU. The KROG-10-01 study used twice the maximal dose used in our study and the 5-FU was given as a bolus (known to have higher rates of toxicity) instead of continuous infusion (as was done in our study).²⁴ The most common toxicities noted in our patients were low-grade gastrointestinal and hematologic. Toxicity did increase with increasing doses of 5-FU, but no DLTs were reported.

In addition, physicians are becoming more comfortable moving away from the traditional 7 to 10 day wait after short-course RT, based on emerging data from the RAPIDO trial and the large meta-analysis showing a benefit to the 4- to 6-week delay in terms of increased pCR without a significant increase in postoperative complications.²⁵ This delay between short-course RT and surgery can be used, as in this study, to accommodate the systemic therapy that was traditionally given postoperatively. Recently, groups in Korea and Iran conducted similar studies, using short-course RT with concurrent chemotherapy followed by consolidative chemotherapy with high rates of pCR (21% and 31%, respectively) and excellent tolerability.^{26,27}

Worldwide, the paradigm for treating locally advanced rectal cancer is shifting to give as much therapy in the neoadjuvant setting as possible to improve rates of response, treat micrometastatic disease, and ensure receipt of systemic therapy. Consistent with prior data, 28.6% (n = 4) of the patients on our study did not complete the

adjuvant FOLFOX regimen, adding impetus to incorporate a total neoadjuvant approach such as is being tested in the PROSPECT and NRG-GI002 studies.

The major limitation of this study is that our pCR rate is low given that the patients with a clinical CR elected to forgo disfiguring surgical procedures. The watch-and-wait strategy is increasingly being used after neoadjuvant chemoradiation, particularly for patients who require abdominoperineal resections.²⁸⁻³⁰ In patients with a clinical CR rate and close surveillance, the outcomes in the literature are as good as for those patients with pCRs. Patients and providers are certainly eager to use this approach and reserve surgery for salvage therapy, and this study shows that short-course RT may be incorporated into this strategy.

Additional limitations of this study include a generally high-risk patient population (>85% T3 and ≈80% node positive with >8% with >4 nodes clinically involved). For the ongoing PROSPECT trial, many of these patients would not have been eligible given the advanced tumor and nodal staging and need for an abdominal perineal surgery upfront. Also, the phase 1 portion of the study escalated the 5-FU to a maximum dose of 200 mg/m², and because there were no DLTs, it is possible that a higher dose may be tolerable and may even be more effective.

Conclusions

Short-course RT with concurrent 5-FU chemotherapy is feasible and well tolerated and may be incorporated into the total neoadjuvant treatment paradigm for locally advanced rectal cancer. These results add to the growing evidence that short-course RT is not only equivalent to long-course RT but may provide additional benefits, such as allowing for a transition to full-dose systemic therapy in the neoadjuvant setting, selective organ preservation in patients with a CR, and providing a more convenient and cost-effective way of delivering pelvic RT.

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