Induction Chemotherapy Reduces Patient-reported Toxicities During Neoadjuvant Chemoradiation with Intensity Modulated Radiotherapy for Rectal Cancer

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Abstract

Based on patient-reported outcomes, a high proportion of patients experienced clinically significant symptoms during pelvic chemoradiotherapy, with diarrhea and urgency being the most commonly reported. Delivery of induction chemotherapy was associated with lower odds of experiencing urgency, bleeding, and tenesmus on patient-reported outcomes during subsequent chemoradiotherapy, with no significant impact on diarrhea and rectal pain.

Background: Initial treatment with either neoadjuvant chemoradiation (CRT) or induction FOLFOX (5-Fluorouracil, leucovorin, and oxaliplatin) chemotherapy followed by CRT is considered standard treatment for locally advanced rectal cancer. We compared patient-reported outcomes (PRO) during CRT in patients who had received induction chemotherapy versus those who did not. **Patients and Methods:** We reviewed records of patients with locally advanced rectal cancer who were treated with CRT between September 2009 and October 2014, and who had completed $\geq$ 4 PRO assessments during treatment. Clinician- and patient-reported toxicities were collected each week during treatment. We fit binomial generalized linear models to maximum toxicity scores across all patients' visits. **Results:** Of 123 patients with $\geq$ 4 PRO assessments, 87 (71%) patients reported a clinically meaningful PRO score of 3 or higher for diarrhea, and 91 (74%) patients reported a PRO score of $\geq$ 3 for urgency, during 1 or more weeks of treatment, corresponding to 'very frequent' or worse. Of 116 patients who had also completed $\geq$ 4 clinician-reported assessments for descriptive analysis, clinically significant diarrhea (Common Terminology Criteria for Adverse Events grade $\geq$ 2) was reported in 9% of patients, and grade 2 proctitis and cystitis were reported in 20% and 4%, respectively. Eighty-four (68%) patients had undergone induction chemotherapy prior to CRT. Patients who received induction chemotherapy had 68% lower odds of experiencing significant urgency (odds ratio [OR], 0.32; 95% confidence interval [CI], 0.11-0.95; $P = .04$), 76% lower odds of bleeding (OR, 0.24; 95% CI, 0.1-0.62; $P < .01$), and 75% lower odds of tenesmus (OR, 0.25; 95% CI, 0.11-0.6; $P < .01$) versus those treated with upfront CRT. **Conclusion:** Based on PROs, a high proportion of patients experienced clinically significant symptoms during pelvic CRT, with diarrhea and urgency being most commonly reported. This appears to be under-reported on clinician-reported assessments. Delivery of induction chemotherapy was associated with

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lower odds of experiencing urgency, bleeding, and tenesmus on PROs during subsequent CRT, with no significant impact on diarrhea and rectal pain.

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Introduction

For over 2 decades, the standard treatment paradigm for locally advanced rectal cancer has been neoadjuvant pelvic radiotherapy (RT) combined with 5-Fluorouracil (5-FU)-based concurrent chemotherapy followed by surgical resection and adjuvant chemotherapy.[1] More recently, induction chemotherapy preceding neoadjuvant chemoradiation (CRT) and surgery has been evaluated in a few small studies, including several prospective phase II trials, which demonstrated the feasibility and promising outcomes for locally advanced rectal cancer with high-risk features based on magnetic resonance imaging (MRI). However, these trials have not focused on the impact of induction chemotherapy on acute toxicity during neoadjuvant CRT.[2-5] Given that induction chemotherapy followed by CRT is now included in the National Comprehensive Cancer Network guidelines as a treatment option for locally advanced rectal cancer, we aimed to evaluate the impact of this sequencing of therapy on the side effects and patient tolerance of CRT.[6]

Acute toxicity during CRT has most commonly been graded by clinicians using scales such as the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer instrument and the National Cancer Institute's Common Terminology for Common Adverse Events (CTCAE).[7] However, patient-reported grading of toxicity has been shown to be more sensitive to a wider range and milder symptoms not captured otherwise by clinician-reported methods, and the patient-reported methods also appear to record higher rates of toxicity.[7-9]

To more accurately assess the impact of induction chemotherapy on our patients' experience during CRT, we evaluated patients' acute toxicity during pelvic radiotherapy as graded by both physician and patients using clinician and patient-reported toxicity grading instruments. We also evaluated potential predictive factors associated with acute toxicity; in particular, we looked at the impact of a more intensive regimen of preoperative therapy with 4 months of induction FOLFOX (5-FU, leucovorin, and oxaliplatin) chemotherapy on the acute toxicity as recorded by patients using a validated patient-reported outcome (PRO) instrument during subsequent CRT.

Patients and Methods

After obtaining a waiver of authorization from our Institutional Review Board, we retrospectively reviewed records of 165 consecutive patients with locally advanced primary rectal cancer who were treated with CRT with intensity modulated radiotherapy (IMRT) between September 2009 and October 2014 at the Memorial Sloan Kettering Cancer Center main campus. This coincided with the time we began collecting weekly PROs from patients undergoing CRT for rectal cancer. All patients had biopsy-confirmed adenocarcinoma by the Memorial Sloan Kettering Cancer Center Department of Pathology. Patients underwent pretreatment staging evaluation consisting of computed tomography[10] of the chest, abdomen, and pelvis; rectal protocol MRI; examination by a colorectal surgeon (including proctoscopy and/or endorectal ultrasound); clinical examination; and routine laboratory testing. Clinical and tumor characteristics were obtained from the medical record and a prospectively maintained database.

Treatment

Chemotherapy. The majority (94.0%) of patients who were treated with induction chemotherapy received 8 standard cycles of FOLFOX administered every 2 weeks. Radiation therapy commenced 2 to 3 weeks after the last planned dose of chemotherapy, and all patients received concurrent chemotherapy in the form of infusional 5-FU 225 mg/m^2 (74.0%) or oral capecitabine 825 mg/m^2 twice daily Monday through Friday (26.0%).

Radiotherapy. All patients underwent CT[10]-based treatment planning in the prone position with intravenous contrast, a full bladder, and immobilization in an Aquaplast mold. The gross tumor volume (GTV) included the primary tumor and enlarged regional nodes based on available clinical information including physical examination, endoscopy, and CT, MRI, and/or positron emission tomography findings. The clinical tumor volume (CTV) included the GTV, rectum, mesorectum, presaccral, internal iliac, and superior rectal lymph nodes based on the RTOG Anorectal Atlas.[11] The external iliac nodal region (CTVB) was included in patients who had T4 disease with anterior invasion. The inguinal nodal region (CTVC) was included in those with T4 disease invading the anal canal. The planning target volume (PTV) was a 5-mm expansion of the CTV. The CTV boost included the GTV, adjacent mesorectum, and presacral space, and PTV boost was a 0.5 cm expansion of the CTV boost. The plans consisted of 5 to 7 equally spaced coplanar fields, and the PTV was treated to 45 Gy in 1.8-Gy fractions with the integrated PTV boost treated to 50 Gy in 2-Gy fractions. All radiotherapy plans met our departmental normal tissue dose constraints (Table 1).

During treatment, a weekly cone beam CT was performed to check setup and bladder distension.

Toxicity and PRO Symptom Assessment

The treating clinician evaluated patients weekly in clinic during CRT, and acute toxicities were graded according to the National Cancer Institute CTCAE v3.0 on a standardized weekly assessment form. Toxicities graded included fatigue, dermatitis, mucositis, nausea, vomiting, diarrhea, proctitis, cystitis, and also vaginal discharge for females.

Symptoms including diarrhea, urgency, rectal pain, bleeding, abdominal cramping, mucus, and tenesmus were assessed on the

Table 1 MSKCC Gastrointestinal Pelvic Normal Tissue Dose Constraints

Structures	Goal	Limit
Small bowel	V45 ≤ 65 cc	V45 > 90 cc
	V50 < 10 cc	V50 > 30 cc
Large bowel	V45 < 135 cc	V45 > 250 cc
	V50 < 45 cc	V50 > 100 cc
Bladder	Mean < 30 Gy	Mean > 32 Gy
	V40 ≤ 40%	V40m > 55%

Abbreviation: MSKCC = Memorial Sloan Kettering Cancer Center.

7-item Bowel Problems Scale (BPS).[12] The BPS questionnaire, which was developed by Clark and Talcott, has been validated and used in prior studies for patients with prostate cancer receiving radiation therapy and in patients with rectal cancer receiving 5-FU-based CRT.[12] The BPS instrument allows patients to report the frequency of diarrhea, urgency, pain, bleeding, cramping, mucus, and tenesmus on a 5-point Likert-type scale ranging from 1, "not at all," to 5, "very frequently" (≥ 3 times/day).

From January 2012, we extended the questionnaire to include 7 additional questions adapted from the National Cancer Institute's CTCAE-PRO modules[13] including skin effects, bloating, gas/flatulence, loss of bowel control, and fatigue and how much these symptoms interfered with usual daily activities.

Patients scored questions on skin effects, bloating, and fatigue from 1 (none) to 5 (very severe). Flatulence was answered as either 1 (yes) or 2 (no). Frequency of loss of bowel control was scored similar to the first 7 questions. Impact of loss of bowel control and fatigue were scored from 1 (not at all) to 5 (very much). Some questions had the option of a sixth choice, which was 'not applicable.'

Excluding the non-applicable score of 6, a clinically meaningful score that may warrant symptomatic management was defined as score ≥ 3.[8]

Of the 165 consecutive patients treated during that time period, 25 patients had completed ≤ 3 PRO assessments and were excluded from the study to ensure that the analysis included those with a high rate of PRO completion. Of the remaining 140 patients, 17 patients underwent 3D conformal RT and were also excluded to allow for homogeneity of RT technique so the effect of induction chemotherapy would not be confounded. Thus, there were 123 patients included in the analysis.

Statistical Analysis

To evaluate factors associated with acute toxicity, as measured by PROs, we fit binomial generalized linear models to max PRO scores across all patients. PROs were coded as binary by ≤ 2 or > 2. Each model was fit with age (≥ 55 or < 55 years), gender, clinical T staging, distance from anal verge, body mass index (BMI), and induction chemotherapy. Models were fit using the glm function in R version 3.13.[14]

Results

Patient, Tumor, and Treatment Characteristics

Table 2 summarizes the patient, tumor and treatment characteristics. Of 123 patients, 66 (53.7%) were male, the majority had clinical T3 node-positive disease, and 84 (68.3%) patients had undergone 5-FU-based induction chemotherapy prior to CRT. Of the patients who received induction chemotherapy, 80 (95%) received FOLFOX, 3 received CAPOX (capecitabine and oxaliplatin), and 1 received FOLFIRI (5-FU, irinotecan, and leucovorin). During CRT, all patients received concurrent 5-FU or capecitabine. One patient required a treatment break, and another missed the last radiation dose and did not complete the full course.

Table 2 Patient, Tumor, and Treatment Characteristics

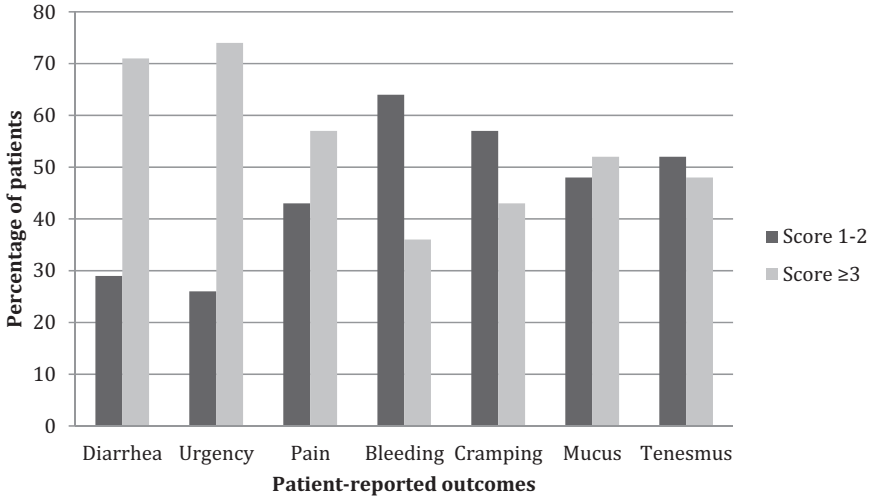
Characteristic	N = 123, n (%)
Median age (range), y	55 (24-89)
Gender	
Male	66 (54)
Female	57 (46)
Median BMI (range), kg/m^2	27.1 (17.3-48.0)
Median KPS (range)	90 (60-100)
Median RT dose (range), Gy	50 (45-56)
Histologic grade	
Well-differentiated	2 (2)
Moderately differentiated	112 (91)
Poorly differentiated	9 (7)
T stage	
T2	14 (11)
T3	94 (76)
T4	15 (12)
N stage	
N0	21 (17)
N1-2	102 (83)
M stage	
M0	119 (97)
M1	4 (3)
AJCC Stage	
Stage I-II	22 (18)
Stage III	97 (79)
Stage IV	4 (3)
Median distance from anal verge (range), cm	7 (0-15)
Induction chemotherapy	
Yes	84 (68)
No	39 (32)
Treatment break	
Yes	2 (2)
No	121 (98)
Completed RT	
Yes	122 (99)
No	1 (1)

Abbreviations: AJCC = American Joint Committee on Cancer; BMI = body mass index; KPS = Karnofsky performance status; RT = radiotherapy.

PROs

Figure 1 displays the frequency of symptoms for the first 7 questions answered by all patients. Eighty-seven (71%) patients

Figure 1 Patient-reported Outcomes for Questions 1 to 7



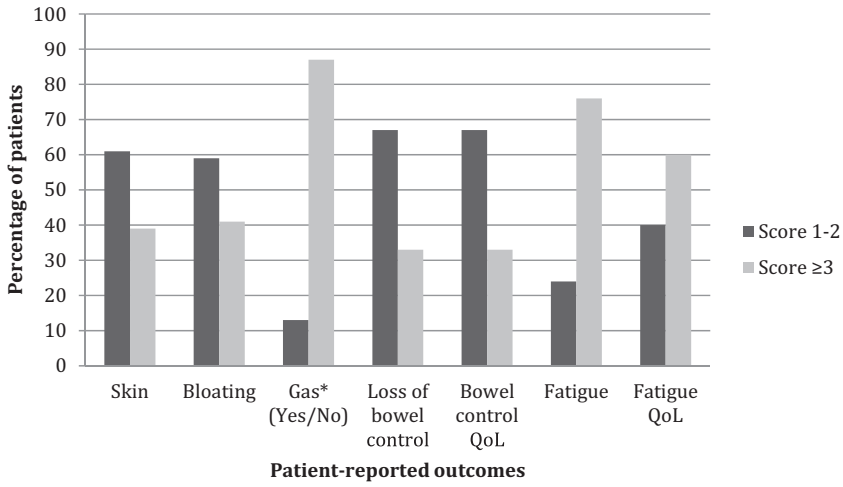
reported a clinically meaningful PRO score of 3 or higher for diarrhea during 1 or more weeks of treatment, corresponding to 'very frequent' or worse, and 91 (74%) patients reported the same score for urgency. About one-half of the patients complained of very frequent rectal pain, tenesmus, and mucus from the rectum (57%, 52%, and 48%, respectively). Fewer experienced rectal bleeding and abdominal cramping (36% and 43%, respectively).

The results of the extended 7 questions answered by 75 of the 123 patients are shown in Figure 2. Thirty-one (41%) patients experienced moderate bloating. Forty-seven (76%) patients reported moderate fatigue, and 45 (60%) patients felt that fatigue had somewhat interfered with usual activities. One-third of patients experienced occasional loss of bowel control that had impacted on usual activities.

Clinician-reported Lower Gastrointestinal and Genitourinary Toxicity

Of the 123 IMRT patients who completed PROs, 116 had also completed 4 or more clinician-reported assessments for descriptive analysis. Clinically significant diarrhea (CTCAE grade $\geq$ 2) was captured in 11 (9%) patients. There were no grade 3 proctitis or cystitis reported on these assessments. Grade 2 proctitis and cystitis were captured in 23 (20%) patients and 5 (4%) patients, respectively.

Figure 2 Patient-reported Outcomes for Questions 8 to 14



Abbreviation: QoL = quality of life. *Symptom was scored as 'yes' or 'no.'.

Factors Associated With PROs

Predictive factors, including age, gender, distance from anal verge, BMI, clinical T staging, and induction chemotherapy, were assessed for association with urgency, bleeding, and tenesmus (Table 3). The most important factor associated with patient-reported acute toxicity during CRT was induction chemotherapy. Patients who received induction chemotherapy had 68% lower odds of experiencing significant urgency (odds ratio [OR], 0.32; 95% confidence interval [CI], 0.11-0.95; $P = .04$), 76% lower odds of bleeding (OR, 0.24; 95% CI, 0.1-0.62; $P < .01$), and 75% lower odds of tenesmus (OR, 0.25; 95% CI, 0.11-0.6; $P < .01$) versus those treated with upfront CRT. Another factor associated with PROs during CRT was older age, where patients 55 and older had 70% lower odds of bleeding (OR, 0.30; 95% CI, 0.12-0.74; $P = .01$). A BMI increase from 20 to 30 appears to increase the probability of pain by about 30% (Figure 3). Above a BMI of 30 to 40, the probability of pain seems to decrease; however, this result is likely owing to the outlying small number of patients with a BMI above 40. For bleeding, as BMI increases from 20 to 35, the probability of bleeding increases about 20%, whereas a BMI above 35 does not present additional risk.

Factors Associated With Clinician-reported Outcomes

Patients 55 or older had 66% lower odds of proctitis than those younger than 55 (OR, 0.34; 95% CI, 0.13-0.92; $P = .03$). There were too few patients that reported grade ≥ 2 diarrhea and cystitis to fit regression models.

Discussion

This study analyzed our large cohort of patients with rectal cancer treated with neoadjuvant CRT, who were evaluated during treatment with standard clinician-based toxicity grading and PROs. We found that the majority of patients experienced symptoms to a level that is considered clinically significant, with diarrhea and urgency being most commonly reported (71% and 74%, respectively). Interestingly, the addition of induction chemotherapy prior to CRT was associated with lower odds of patients experiencing clinically significant bleeding, urgency, and tenesmus (76%, 68%, and 75%, respectively). Urgency and tenesmus would not have been captured on the standard clinician-reported adverse events assessment form, and the reduction in these symptoms associated with induction chemotherapy might not have been identified, which further emphasizes the clinical importance of collecting PROs.

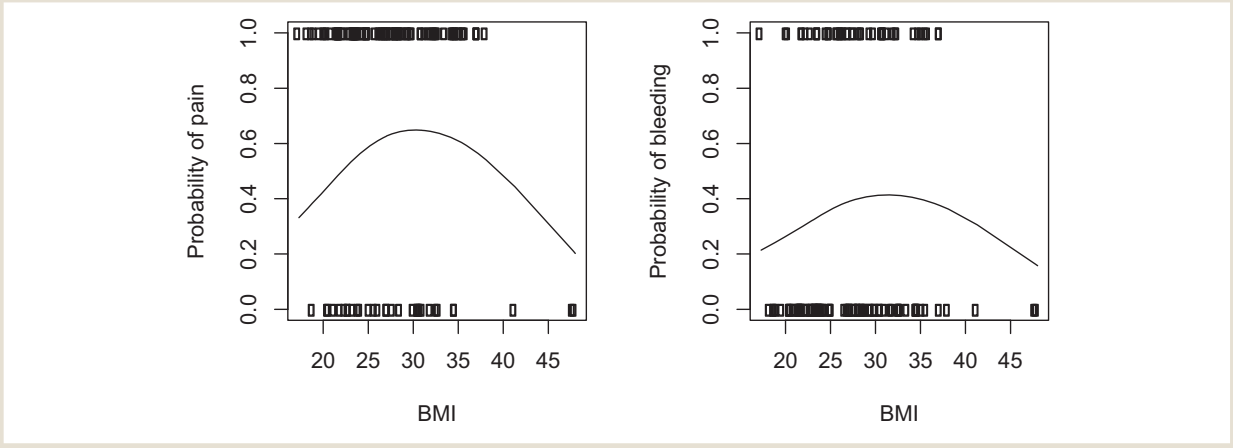
Theoretically, early delivery of systemic chemotherapy aims to prevent or reduce existing distant micrometastatic disease that may impact disease-free and overall survival. Initially, there was some concern that induction chemotherapy would potentially increase acute toxicity during CRT, given that patient would have had a reduced tolerance of therapy after receiving 4 months of aggressive chemotherapy. However, it appears that there may be a benefit of upfront chemotherapy on tolerance of CRT as a result of tumor response that leads to tumor downgrading, a decrease in rectal bleeding, and potentially less of an inflammatory response to radiotherapy that is often the cause of rectal pain, urgency, and tenesmus during treatment. In addition, the reduced tumor size potentially allows for a smaller target required for the radiotherapy boost.

Table 3 Parameter Estimates From Binomial Generalized Linear Models for Diarrhea, Proctitis, and Cystitis

Parameters	Urgency				Bleeding				Tenesmus			
	OR	LCL	UCL	*P*	OR	LCL	UCL	*P*	OR	LCL	UCL	*P*
Age ≥ 55 y	0.83	0.35	2.00	.68	0.30	0.12	0.74	.01	0.80	0.36	1.78	.59
Female	1.27	0.53	3.07	.60	0.73	0.31	1.74	.48	0.66	0.30	1.43	.29
Distance from anal verge	0.96	0.85	1.08	.48	1.03	0.93	1.15	.56	1.01	0.91	1.12	.92
BMI	0.96	0.89	1.03	.22	2.02	0.98	1.00	.07	1.01	0.94	1.08	.81
BMI-2	NA	NA	NA	NA	0.99	0.98	1.00	.09	NA	NA	NA	NA
Clinical T3 stage	1.42	0.38	5.34	.60	2.2	0.51	9.49	.29	2.51	0.69	9.03	.16
Clinical T4 stage	1.29	0.24	7.04	.77	3.8	0.65	22.24	.14	2.32	0.46	11.62	.31
Induction chemotherapy	0.32	0.11	0.95	.04	0.24	0.10	0.62	<.01	0.25	0.11	0.60	<.01

Abbreviations: BMI = body mass index; LCL = lower 95% confidence limit; OR = odds ratio; UCL = upper 95% confidence limit.

Figure 3 Relationship Between BMI and Probability of Rectal Pain and Bleeding Using Cubic Smoothing Splines



Abbreviation: BMI = body mass index.

Although several prospective studies have evaluated the use of induction chemotherapy followed by CRT for high-risk, locally advanced rectal cancers, these studies primarily focused on the impact of the induction chemotherapy on pathologic complete response (pCR) rates and the impact on disease-free survival. Chau et al reported on a single-arm phase II study of induction CAPOX followed by CRT in patients with rectal cancer with high-risk MRI features. These investigators showed an objective tumor response in 88% of patients after chemotherapy and symptomatic responses in 86% of patients with a median of 32 days (ie, just over 1 cycle of CAPOX).[3]

The Spanish GCR-3 trial was a randomized phase II study of 108 patients comparing preoperative CRT with capecitabine, oxalipatin, and concurrent radiation followed by surgery and adjuvant CAPOX (arm A) with induction CAPOX followed by CRT and surgery (arm B).[4] Their results showed that induction CAPOX before CRT did not improve surgical outcomes, including pCR, tumor regression, downstaging, and R0 resection. However, this study demonstrated that the administration of CAPOX as induction chemotherapy improves treatment compliance and confers lesser toxicity than in the adjuvant setting.[4,15,16] No significant differences were found between the arms in number of patients with grades 3 to 4 toxicity during CRT itself; however, during adjuvant or induction chemotherapy, significantly more patients had grade 3 to 4 toxicity in the adjuvant arm than in the induction arm (54% vs. 19% induction; $P = .0004$). It was also found that the proportion of patients who received all 4 cycles of chemotherapy was significantly higher in those who received as induction treatment as compared with the adjuvant setting (94% vs. 57% adjuvant; $P < .0001$). The suboptimal adherence to adjuvant chemotherapy was also confirmed by Fernandez-Martos et al,[4] which supports the notion that upfront chemotherapy may decrease acute toxicity experienced as compared with the postoperative setting. Another small randomized phase II trial from Belgium showed that short course induction chemotherapy with 2 cycles of modified FOLFOX followed by CRT did not appear to impact on ypT0-1N0 rate as compared with standard preoperative CRT alone, and rates of grade 3 to 4 toxicity were similar between the 2 arms during preoperative CRT.[5] It is possible that the impact on toxicity during the concurrent CRT component of therapy in these studies may have been mitigated by the use of oxaliplatin as part of the concurrent chemotherapy regimen in this study, which has since been shown to contribute to increased toxicity when used during CRT.[17,18]

Our institution recently reported an updated retrospective review investigating induction FOLFOX followed by radiotherapy with concurrent infusional 5-FU or capecitabine, and then surgical resection in 308 patients with rectal cancer and compared the response rates and tolerance of FOLFOX to 320 patients who had standard neoadjuvant CRT followed by surgery and adjuvant FOLFOX. This retrospective study demonstrated that 36% who received total neoadjuvant therapy achieved a CR, including both pCR in those who underwent surgery and sustained clinical CR (cCR) for at least 12 months posttreatment in those who did not undergo surgery as compared with 21% in the CRT with planned adjuvant chemotherapy cohort.[2,19] With the upfront chemotherapy regimen, many patients reported rapid relief of symptoms, such as rectal pain and bleeding, frequently in the first week of induction chemotherapy similarly demonstrated by Chau et al. It is possible that upfront chemotherapy could potentially achieve faster control of tumor-related symptoms compared with initial CRT, which can lead to initial inflammation and worsening of tumor-related pain and tenesmus.

In our analysis of predictive factors for acute toxicity, we also found that patients who were 55 years or older had lower odds of experiencing clinically significant proctitis and rectal bleeding compared with similar younger patients. Physiological studies have shown that even in the absence of disease, age-related changes have effects on anorectal function including reduced rectal sensation especially in females, which may explain this result.[20,21]

Our study is the first and largest to our knowledge that described PROs in patients with rectal cancer treated with CRT using IMRT planning. We also compared the acute toxicities reported by our

patients with the standard physician reporting of CTCAE grading. It was reassuring to see that the cumulative incidence of patients who ever experienced diarrhea during treatment was fairly similar on clinician-reported assessments (83%) and PROs (90%). However, there was a larger difference noted for proctitis (85% clinician-reported vs. 71% patient-reported), and it is interesting that the prevalence was captured more by clinicians than reported by patients. For clinically significant cutoffs, the cumulative incidences of diarrhea and proctitis were reported much more frequently on PROs than clinician-reported assessments (diarrhea, 26% PROs vs. 9% clinician; proctitis, 42% PROs vs. 20% clinician). A recent systematic review comparing PROs and clinician toxicity reporting in randomized controlled trials of rectal cancer had demonstrated that PROs reported higher rates of toxicity symptoms than clinician-reported assessments and also reported on a wider range of symptoms, including bleeding, urgency, tenesmus, abdominal cramping, flatulence, and loss of bowel control, which were not assessed by clinician-reported toxicity.[7] They also give an indication of the impact of some symptoms on patients' quality of life. The results of our study support this, and also suggest that PROs may be even more useful and sensitive in capturing symptoms when more severe, requiring medical attention.

One of the limitations of our analysis is that it is a retrospective review of our prospectively collected physician- and patient-reported acute toxicity assessments, and therefore, we had to address the issue of missing data points. We excluded 25 patients owing to missing PROs. We also did not collect patient-reported data on urinary or sexual functions, which may also be important factors that impact quality of life. Another limitation is that we did not collect dosimetric data to correlate with the PROs, but all plans among patients treated with or without induction chemotherapy met the departmental normal tissue dose constraints.

Conclusion

Our analysis demonstrated that the delivery of induction chemotherapy followed by CRT was associated with lower odds of experiencing urgency, bleeding, and tenesmus than with upfront CRT for patients with locally advanced rectal cancer. These findings further support this sequencing of therapy given the benefit of reducing acute toxicity during CRT and ultimately improving quality of life during treatment. Furthermore, the addition of PRO assessments during CRT for rectal cancer further refine the ability to assess toxicity during therapy. Collecting PROs during treatment may enhance clinician-patient communication and aid in effective symptom management. PROs are being increasingly recognized as an important tool during a patient's treatment that complements clinician-reported assessments. The use of PROs improve physician-patient communication, aiding clinicians in treatment decisions, which in turn improves a patient's quality of life during treatment.

Clinical Practice Points

- Our study assessed the impact of induction chemotherapy during treatment for locally advanced rectal cancer on patients' experience during CRT as measured on clinician-reported outcomes and PROs. We also evaluated potential predictive factors associated with acute toxicity, in particular, the impact of a more intensive regimen of preoperative therapy with 4 months of FOLFOX induction chemotherapy on acute toxicity as measured on PROs.
- This has relevant impact in the current literature as previously conducted small studies and prospective phase II trials demonstrated the feasibility and promising outcomes with this induction chemotherapy; however, these studies had not focused on the impact of this regimen on acute toxicity during neoadjuvant CRT.
- Interestingly, our findings show that the addition of induction chemotherapy prior to CRT was associated with lower odds of patients experiencing clinically significant bleeding, urgency, and tenesmus. We believe that our study further supports this sequencing of therapy, which appears to give patients the benefit of toxicity reduction during CRT and ultimately improves quality of life during treatment.

Disclosure

The authors have stated that they have no conflicts of interest.

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