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The Impact of Surgical Diversion Before Neoadjuvant Therapy for Rectal Cancer

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Abstract

Up-front fecal diversion can palliate emergent symptoms related to locally advanced rectal cancer (LARC) allowing patients to receive neoadjuvant chemoradiation therapy (nCRT). We analyzed outcomes of pretreatment-diverted LARC patients relative to nondiverted patients to define the impact of this management strategy. We retrospectively collected data on 103 LARC patients treated with nCRT and surgery. Medical records were reviewed for patient characteristics, staging, treatment plan, and outcomes. Thirteen LARC patients underwent pretreatment diversion for urgent symptoms and 90 LARC patients proceeded directly to nCRT. In all, 50 per cent of diverted patients presented with T4 tumor compared with 14 per cent in the nondiverted patients ($P=0.003$). Diverted patients experienced a delay in time-to-treatment initiation of 12 days, although this difference was not statistically significant. Similar rates of chemoradiation and surgical toxicities were observed. Even though diverted patients demonstrated less pathologic response to nCRT compared with nondiverted patients ($P=0.04$), there was no significant difference in overall survival. In conclusion, our study demonstrates the effectiveness of up-front fecal diversion at managing emergent obstructive symptoms related to advanced rectal cancer without additional complications, allowing patients to proceed with nCRT followed by radical surgery.

Neoadjuvant chemoradiation therapy (nCRT) followed by radical resection has become accepted as an appropriate therapeutic strategy for locally advanced rectal cancer (LARC) based on beneficial results demonstrated in various randomized and Phase II clinical trials. ^{1–3} nCRT has many established advantages over adjuvant therapy in the management of LARC including improved treatment tolerance with increased likelihood to complete

therapy, increased sphincter preservation with tumor downstaging, and the ability to assess tumor response to chemoradiation.^{1, 2, 4-6}

Total mesorectal excision (TME) has become the standard resection technique for LARC, allowing sphincter preservation whereas minimizing local recurrence rates compared with alternative surgical approaches.⁶⁻⁹ This technique, however, has been associated with higher rates of anastomotic leakage, which can lead to significant morbidity or mortality and increase the length of hospital stay.¹⁰⁻¹² The creation of a diverting stoma in conjunction with the TME procedure aims to prevent pelvic sepsis by allowing time for the anastomosis to heal before being subjected to the stresses of postoperative bowel movement and functioning.¹³ Fecal diversion may also decrease the clinical consequences and severity of intra-abdominal sepsis resulting from an anastomotic dehiscence.^{10, 13-15}

Although stoma creation many times occurs at the conclusion of the TME procedure, many patients with advanced primary rectal tumors present with severely debilitating symptoms that must be addressed at initial presentation. Approximately 15 per cent of patients with colorectal cancer present with signs of large bowel obstruction.¹⁶ Severe symptoms such as obstruction associated with LARC tumors can be palliated with up-front fecal diversion before initiating nCRT. The advantage of this approach is that, in addition to preventing the complications associated with stresses of postoperative bowel movement and functioning, as described above, it alleviates the need to immediately resect an obstructing rectal tumor. This allows patients to proceed with standard nCRT strategies and subsequent elective radical resection. The disadvantage of up-front fecal diversion is the necessary time delay for nCRT initiation and surgical treatment of the primary tumor as a result of the recovery time needed after the creation of an up-front diverting stoma.¹⁶

Although the rationale for up-front fecal diversion is to allow for optimal nCRT and surgical treatment of the primary tumor, the clinical impact of this therapeutic strategy is not well defined. The objective of this study was to compare outcomes in patients requiring fecal diversion before treatment of LARC with patients who proceeded directly to nCRT followed by radical resection.

Methods

Patient Population

This is a single-institution Institutional Review Board approved retrospective study of LARC patients diagnosed between 1996 and 2010 and treated at the Medical University of South Carolina (MUSC) with nCRT followed by planned radical resection. Using the MUSC Tumor Registry and computerized records, subjects for the study were identified using the following criteria: 1) initially AJCC stage 2 or 3 rectal cancer (T3/T4 and/or node positive), 2) received nCRT followed by radical resection, and with 3) no evidence of distant metastatic disease preoperatively or at surgery. Computerized medical records including operative, pathologic, radiology, and laboratory reports, and clinic progress notes were reviewed to obtain demographic, patient characteristics, tumor staging, treatment plan, and outcome data.

Initial Evaluation and Treatment

Pretreatment tumor-node-metastasis (TNM) staging was determined based on endoscopic ultrasound, CT, and/or MRI reports. The need for pre-nCRT diversion was determined by the treating surgeon with assistance from the medical and radiation oncologists. Nondiverted patients were those individuals that proceeded directly to nCRT followed by radical resection. All patients received 5-fluorouracil based chemoradiation. Posttreatment restaging was evaluated at the discretion of the treating clinician. Resectable patients then underwent proctectomy typically 8 weeks after the completion of nCRT. Surgical approach after nCRT was decided by the treating surgeon.

Pathologic Evaluation and Response

Posttreatment tumor stage was determined upon pathologic review of final surgical specimens and staged according to the TNM classification. Response rates were determined by comparing the pretreatment radiologic-derived stage to the posttreatment histologic stage. This is an accepted approach to assess tumor response and has been published as a response predictor in recent literature.^{17–19} Complete response (CR) to nCRT was defined as the absence of residual carcinoma on final surgical specimen. Partial response (PR) was defined as downstaging by two or more T-stages and/or one or more nodal stages. No response was considered as downstaging by less than two T-stages and/or no nodal downstaging. A single patient refused surgery after receiving nCRT and was considered a clinical CR based on clinical and radiographic findings.

Statistical Analysis

Fisher's exact test and Wilcoxon rank-sum test were used to examine associations between diversion status and categorical and continuous patient characteristics, respectively. Time-to-treatment (TTT) initiation was defined as the time from diagnosis to start of nCRT. Overall survival was defined as the time from diagnosis to death from any cause within two years of treatment completion. Two-year survival was analyzed, so posttreatment data would be uniform for all patients. Graphical displays of TTT initiation and overall survival were constructed using Kaplan-Meier methods, and comparisons between diverted and nondiverted patients performed using log-rank tests. Comparisons of toxicity and surgical complication rates between diverted and nondiverted patients were conducted using Fisher's exact test.

Results

Demographics

One hundred and three LARC patients were identified on review of the medical records that met the analysis criteria and were included in the study. Thirteen LARC patients underwent pretreatment fecal diversion after the initial assessment by the surgical team and 90 LARC patients proceeded directly to nCRT (Table 1). The reasons for palliative surgery for diverted patients included: symptomatic complete or nearly complete obstruction (nine patients), tumor perforation into the bladder wall (two patients), or the presence of fistula (two patients). The types of diversion performed in these 13 patients were loop colostomy (nine

patients), end colostomy (two patients), and ileostomy (two patients). Nondiverted patients were significantly older than diverted patients, with median ages of 63 and 51 years, respectively ($P = 0.003$). Tumor stage was significantly associated with diversion status with 42 and 50 per cent of diverted patients with tumor stages T3 and T4, compared with nondiverted rates of 85 and 14 per cent, respectively ($P = 0.003$). The findings of advanced T-stage in the diverted patients demonstrate that these symptomatic patients presented with more advanced primary tumors compared with the nondiverted group. In contrast, nodal stage was not associated with diversion status ($P = 0.47$). Radiation dose did not differ significantly between the two groups ($P = 0.56$).

Time to Treatment Initiation

Adequate follow-up data for determination of TTT initiation was available for 57 nondiverted and 12 diverted patients. Diverted patients experienced a similar TTT initiation relative to nondiverted patients ($P = 0.128$) (Fig. 1). Median TTT initiation for nondiverted patients was 32 days (interquartile range = 20–52 days), whereas median TTT initiation for diverted patients was 44 days (interquartile range = 26.25–63.75 days).

Response Rates

Ninety-four patients were evaluable for response, including one patient observed to have a complete clinical response after nCRT who subsequently refused surgery; three patients deemed unresectable and classified as nonresponders; and 90 patients known to have undergone surgical resection. Documentation of surgery was missing for six patient records, and therefore response was not evaluable for these patients.

Based on posttreatment TNM staging, diverted patients demonstrated less treatment response to nCRT compared with nondiverted patients. Comparing the diverted with the nondiverted patients, CR rates (0% vs 20%) and nonresponse rates (85% vs 47%) were statistically different ($P = 0.04$; Table 2). Comparing patients who demonstrated downstaging after nCRT (either CR or PR), response was significantly decreased in the diverted group relative to nondiverted patients (15% vs 53%; $P = 0.02$). Given the differences observed in pretreatment T-stage with increased T4 disease in the diverted group, the decreased response observed in the diverted group may be attributed to the advanced disease at presentation. Despite these differences in response, overall survival was not significantly different with 2-year survival rates of 69 per cent (95% confidence interval = 48%–100%) for the diverted group compared with 66 per cent (95% confidence interval = 56%–77%) for the nondiverted patients ($P = 0.95$).

Complication Rates

Neoadjuvant chemoradiation toxicity and surgical complication rates were also studied between diverted and nondiverted patients. Chemoradiation toxicity data were gathered and there was no relationship between diversion and toxicity grade ($P > 0.99$; Table 3). High toxicity (grade II and above) was observed in 46 per cent of patients in the diverted group and 44 per cent of patients in the nondiverted group ($P > 0.99$). In addition, there was no significant difference in surgical complication rate between groups at time of radical

resection, with 25 per cent of diverted patients having surgical complications as compared with 42 per cent of nondiverted patients ($P = 0.35$; Table 4).

Discussion

The use of nCRT in the management of LARC has been proven to decrease local recurrence rates, improve sphincter preservation with tumor downstaging, and provide the ability to assess tumor response to chemoradiation.^{1, 2, 4-6} However, LARC patients can present with emergent symptoms of obstruction that must be addressed before undergoing treatment of the primary cancer. Up-front fecal diversion is a temporary measure used to alleviate the acute symptoms of obstruction in order for patients to receive nCRT followed by radical resection.¹⁶ The goal of our analysis was to assess whether initial diversion and subsequent nCRT and radical surgery is a safe and oncologically effective treatment strategy for LARC patients presenting with urgent symptoms such as obstruction.

Our investigation demonstrated that despite the advanced T-stage at presentation and associated decreased response to nCRT observed in the diverted patients, an up-front diversion treatment strategy resulted in equivalent short-term survival with no differences in treatment-associated complications. These results demonstrate that pre-nCRT stoma creation provided the palliative benefits of fecal diversion without compromising the oncologic treatment strategy and patient safety.

The balance of immediately treating the underlying cause of emergent symptoms, while minimizing the delay of nCRT is of great importance. In our study, the surgical strategy used in the majority of LARC patients requiring diversion was an open minimally invasive loop transverse colostomy created through a single transverse incision in the right upper quadrant. This surgical strategy avoids a midline incision and pelvic dissection. In the majority of cases, the diverting stoma was left in place at the time of radical resection serving to protect the new anastomosis. In comparison, the majority of patients receiving nCRT without up-front diversion received a protecting loop ileostomy at the time of radical resection when GI continuity was restored. Thus, except for the up-front urgent surgery without significant delay in subsequent therapy, the treatment strategies for our populations investigated was similar.

A recent study from Washington University demonstrated that up-front nCRT without diversion is a safe strategy for endoscopically (noncompletely) obstructed patients undergoing LARC therapy.¹⁶ Similar to our findings, they demonstrated that symptomatic tumors tended to be larger and have a higher T-stage. In this study, patients demonstrating complete malignant bowel obstruction or clinical symptoms of obstruction were excluded. The authors concluded that diversion could be avoided in patients without signs or symptoms of complete obstruction. Our study explored the management of patients with more acute symptoms such as large bowel obstruction. In this population, diversion effectively palliated the symptoms and allowed patients to proceed with the oncologic therapy without significant delay. Our study compliments the previous report by highlighting a therapeutic strategy for LARC patients presenting with urgent symptoms. Taken together, evidence demonstrates that diversion can be avoided in the majority of LARC patients

including asymptomatic patients with endoscopic evidence of obstruction. However, LARC patients presenting with acute symptoms such as obstruction, and diversion can be a means for palliation that allows patients to receive nCRT.

Limitations of our study include the small number of diverted patients analyzed as well as the retrospective nature of the analysis. Our study could not control for the inherent differences in characteristics between the diverted and nondiverted patients such as age and primary T-stage. For example, in comparing therapeutic response rates to nCRT, the difference in T-stage at presentation in the populations likely influenced the decreased response observed in the diverted population. Ideally, prospective designed studies including larger number of patients would more effectively address the impact on therapeutic response.

Taken together, the results of our study demonstrate the effectiveness of up-front fecal diversion at managing emergent symptoms such as obstruction associated with LARC allowing patients to proceed with nCRT followed by radical surgery.

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FIG. 1.
Kaplan-Meier estimates of the TTT initiation (days) based on data from 57 nondiverted and 12 diverted subjects.

Table 1

Characteristics of Diverted and Nondiverted Patients

Variable	Diverted (<i>n</i> = 13)		Nondiverted (<i>n</i> = 90)		<i>P</i> value [‡]
	Number [*]	Descriptive Measure [‡]	Number [*]	Descriptive Measure [‡]	
Gender					0.52
Female	5	38	25	28	
Male	8	62	64	72	
Race					0.38
African-American	5	38	19	21	
White	8	62	69	78	
Asian	0	0	1	1	
N-stage					0.47
N0	6	60	41	48	
N1	3	30	39	46	
N2	1	10	5	6	
T-stage					0.003
T2	1	8	1	1	
T3	5	42	72	85	
T4	6	50	12	14	
Age (years)	13	51 (25–62)	83	63 (29–83)	0.003
Radiation dose (Gy)	11	50.4 (50–59.4)	54	52.75 (25–55.8)	0.56

* Variable-specific frequencies may not total sample size due to missing data.

[‡] Descriptive measures for categorical and continuous variables are column per cent and median (range), respectively. Column percentages may not total 100% due to rounding.

[‡] *P* values for categorical variables based on Fisher's exact test. *P* values for continuous variables are based on Wilcoxon rank-sum test.

Table 2

Response Rates for Diverted and Nondiverted Patients					
	Diverted (<i>n</i> = 13)		Nondiverted (<i>n</i> = 90)		<i>P</i> value
	Number	Per cent	Number	Per cent	
Response					0.04
Complete (CR)	0	0	16	20	
Partial (PR)	2	15	27	33	
None (no response)	11	85	38	47	
Overall (CR + PR)	2	15	43	53	0.02

Table 3
Neoadjuvant Chemoradiation Toxicity Rates for Diverted and Nondiverted Patients

	Diverted (<i>n</i> = 13)		Nondiverted (<i>n</i> = 90)		<i>P</i> value
	Number	Per cent	Number	Per cent	
Toxicity					>0.99
None	5	38	36	40	
Grade I	2	15	14	16	
Grade II	6	46	35	39	
Grade III	0	0	4	4	
Grade IV	0	0	1	1	

Table 4

Surgical Complication Rates for Diverted and Nondiverted Patients

	Diverted (<i>n</i> = 12)		Nondiverted (<i>n</i> = 81)		<i>P</i> value
	Number	Per cent	Number	Per cent	
Complication					0.35
Yes	3	25	34	42	
No	9	75	47	58	