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Preoperative chemoradiation for rectal cancer: results of multimodality management and analysis of prognostic factors

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Abstract

Background: Our goals were to examine the impact of neoadjuvant chemoradiation for rectal cancer on surgical outcomes and to determine prognostic factors predicting improved survival.
Methods: Retrospective cohort of 56 male and 44 female patients.
Results: After preoperative chemoradiation, 73% of patients had sphincter-preserving surgery. The 5-year disease-free (DFS) and overall survival rates were 77% and 81%, respectively. Twenty-five percent of patients showed a complete pathologic response. T-level downstaging and pathologic T stage did not correlate with recurrence or survival rates. Pathologic nodal stage was associated with a significant difference in recurrence rates (N_0 19%, N_1 20%, and N_2 75%, $P = .038$) and DFS (N_0/N_1 vs. N_2, 79% vs. 25%, $P = .002$).
Conclusion: Neoadjuvant chemoradiation resulted in a high rate of sphincter preservation. Complete pathologic responses after surgery were frequent and although pathologic T stage after surgery did not affect recurrence rates, pathologic nodal response was associated with improved recurrence and survival rates.

Keywords: Neoadjuvant chemoradiation; Rectal cancer; Rectal surgery

Despite improvements in screening protocols, surgical techniques, and adjuvant therapy, carcinoma of the rectum remains one of the leading causes of cancer-related morbidity and deaths in the United States. It is estimated that approximately 40,000 patients will be diagnosed with rectal cancer in 2006, and the management of these patients is focused both on long-term cure as well as sphincter-preservation [1]. Treatment of patients with this malignancy continues to present multiple challenges for the gastrointestinal surgeon.

Controversies exist with regard to the selection of patients with low rectal cancers for sphincter-preserving operations and the role of extended mesorectal lymph node dissections. Neoadjuvant chemoradiation for locally advanced rectal cancer is widely accepted as the standard treatment, despite the lack of convincing data from randomized clinical trials. Reported rates of sphincter preservation after neoadjuvant chemoradiation vary widely, and the impact of treatment response on survival is highly controversial. Previous reports have attempted to identify clinical and pathologic factors associated with risk for recurrence after neoadjuvant therapy. These studies have had conflicting results in terms of identifying independent prognostic predictors of survival. The goals of this study were to examine the impact of preoperative treatment on surgical morbidity, mortality, and its effect on the ability to perform sphincter-preserving operations. We also sought to identify factors that affect disease-free survival (DFS) and overall survival (OS) in patients receiving multimodality therapy for rectal carcinoma.

Methods

The medical records of 152 patients who were diagnosed and treated for rectal adenocarcinoma at Northwestern Me-

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morial Hospital were reviewed. We excluded all cases with incomplete records or incomplete follow-up. Patients undergoing palliative resections for stage IV disease were also excluded from the analysis. Patients referred for surgical therapy but who did not receive their preoperative therapy at Northwestern were not included in the overall analysis. Thus, the final study population comprised 100 patients who were treated for rectal cancer between 1992 and 2002.

Pretreatment clinical staging was performed by using a combination of physical examination, cross-sectional imaging with either computed tomography or magnetic resonance imaging scan and endoscopic ultrasound. Indications for neoadjuvant therapy were full-thickness tumors (T_3) and/or node-positive disease. All patients received 5-fluorouracil (r-FU)-based chemoradiation with the majority of patients receiving a total dose of 5,040 cGy of pelvic irradiation. Radiotherapy usually began the first day of chemotherapy and was administered 5 times per week with a daily fraction of 180 cGy. Patients were treated with megavoltage radiation using 3- or 4-field techniques. Occasionally, additional fields were used to cover inguinal nodes because of tumor proximity to the anal verge. The initial pelvis field was treated to a median dose of 4,500 cGy (range, 3,960–5,040 cGy). Most patients received a boost for a median total dose of 5,040 cGy (range, 3,960–6,140 cGy). Patients received either concurrent low-dose continuous infusional 5-FU (88%) or bolus 5-FU (12%) during radiation. Postoperative chemotherapy was not routinely given within the timeframe of this analysis. Surgical treatment was performed 4 to 8 weeks after the completion of neoadjuvant chemoradiation. Pathologic staging of the patients was performed according to the postoperative pathology report by using the standard tumor-node metastasis system.

Standard demographic data gathered from the medical records included age, race, and sex. Operative reports were reviewed for type of resection and anastomosis performed and extent of lymph node dissection. For the purpose of this study, curative resection was defined as resection of all gross disease with no evidence of distant metastases and negative histological resection margins. All histopathologic slides were reviewed by a single pathologist to confirm the diagnosis of adenocarcinoma and to ensure consistent and accurate classification of several pathologic variables. These variables included tumor location and grade, extent of residual primary tumor after neoadjuvant therapy, and number of positive lymph nodes. Outcome measures included disease-free survival and overall survival. Disease-free survival was calculated from the time chemoradiation started to first documented recurrence. Overall survival was calculated from the time chemoradiation started to either death or most recent contact. Statistical analysis was performed by using SAS (version 9.0; SAS, Cary, NC). Survival within groups was analyzed by means of the Kaplan-Meier method with differences compared by use of log-rank tests [2]. Variables shown to be of statistical significance in univariate survival analysis were further assessed by Cox multivariate analysis [3]. OS and DFS medians were presented with 95% confidence intervals. Results from the proportional hazards models were summarized by giving hazard ratios along with 95% confidence intervals.

Table 1
Clinical and pathologic characteristics (n = 100)

Variable	Data
Median age, y (range)	61 years (24–86 y)
Sex (male/female)	56/44
Presenting symptoms (%)	
Rectal bleeding	84
Change in bowel habits	57
Weight loss	17
Asymptomatic	8
Tumor location	
Distal rectum	64
Middle rectum	33
Proximal rectum	3
Tumor differentiation	
Well differentiated	8
Moderately well differentiated	81
Poorly differentiated	11
Pretreatment clinical stage	
T_1	1
T_2	16
T_3	80
T_4	3
N_0	47
N_1	41
N_2	12
Operative procedures	
Proctocolectomy with coloanal anastomosis	38
Low anterior resection with colorectal anastomosis	33
Abdomino-perineal resection	27
Total proctocolectomy with J-pouch ileoanal anastomosis	2
Postoperative pathologic stage	
T0	25
T1	40
T2	16
T3	19
N_0	72
N_1	22
N_2	6

Differences at $P < .05$ were considered statistically significant.

Results

Clinical presentation

The study group included 56 male and 44 female patients (Table 1). The median age of the patients was 61 years (range, 24–86 years). The most common symptoms were rectal bleeding (84%), followed by change in bowel movements (57%) and weight loss (17%). More than 50% of patients had more than 1 symptom. Tumor location was defined by the distal most location of visible tumor. Distal, middle, and proximal rectum were defined at 0 to 8 cm, 8 to 12 cm, and 12 to 16 cm from the anal verge, respectively, based on proctoscopic examination performed by the treating surgeon. Tumor location was low rectal 64%, midrectal 33%, and upper rectum 3%. Pretreatment T stage and N stage are listed in Table 1. Pretreatment clinical staging showed T_3 lesions in 80% and N-positive disease in 53%.