Diseases of the Colon & Rectum

Complete Pathologic Response Following Preoperative Chemoradiation Therapy for Middle to Lower Rectal Cancer Is Not a Prognostic Factor for a Better Outcome

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PURPOSE: The aim of this study was to evaluate factors associated with pathologic tumor response following preoperative chemoradiation therapy, and the prognostic impact of pathologic response on overall and disease-free survival. METHODS: Between 1994 and 2002, 132 patients underwent chemoradiation therapy followed by surgery for middle to lower rectal cancer. After excluding 26 cases (metastatic cancer, n = 13; nonradical surgery, n = 6; local excision procedure, n = 4; non-5-fluorouracil-based chemotherapy, n = 2; incomplete data on preoperative chemoradiation therapy regimen used, n = 1), the remaining 106 patients were included in the study. Variables considered were the following: age, gender, tumor location, pretreatment T and N stage, modality of 5-fluorouracil administration, total radiotherapy dose delivered, chemoradiation therapy regimen used (Regimen A: chemotherapy (bolus of 5-fluorouracil and leucovorin, days 1–5 and 29–33) + radiotherapy (45 Gy/25 F/1.8 Gy/F); Regimen B: chemotherapy (5-fluorouracil continuous venous infusion ± weekly bolus of carboplatin or oxaliplatin) + radiotherapy (50.4 Gy/28 F/1.8 Gy/F)), time interval between completion of chemoradiation therapy and surgery, postoperative chemotherapy administration, surgical procedures, pT, pN, and pTNM stage, and response to chemoradiation therapy defined as tumor regression grade, scored from 1 (no tumor on surgical specimen) to 5 (absence of regressive changes). Statistical analysis was performed by means of logistic regression analysis (Cox's model for overall and disease-free survival). RESULTS: Median age of the 106 patients was 60 (range, 31–79) years and the male:female ratio, 66:40. Median distance of tumor from the anal verge was 6 (range, 1–11) cm. Pretreatment TNM stage, available in 104 patients, was cT3–T4N0, n = 41; cT2N1, n = 9; cT3N1, n = 39; and cT4N1, n = 17. The median radiotherapy dose delivered was 50.4 (range, 40–56) Gy; 58 patients received 5-fluorouracil by continuous venous infusion, and carboplatin with oxaliplatin was added to the chemotherapy schedule in 71 cases. Patients were given Regimen A in 47 cases and Regimen B in 59. The median interval between chemoradiation therapy and surgery was 42.5 (range, 19–136) days, and 94 patients underwent a sphincter-saving procedure. Tumor regression grade, available in 104 cases, was 1, n = 19; 2, n = 18; 3, n = 15; 4, n = 13; and 5, n = 39. At a median follow-up of 42 (range, 1–110) months, 11 patients had died, and 95 were alive. None of the patients had local recurrences, but 13 had distant recurrences. At logistic regression analysis, the chemoradiation therapy regimen used was the only independent predictor of tumor response following preoperative chemoradiation therapy (odds ratio = 0.29, 95% confidence interval = 0.13–0.67, $P = 0.003$). At Cox's regression analy-

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sis, pretreatment T stage was the only independent prognostic factor for both disease-free survival (relative risk = 7.13, 95% confidence interval = 2.3–21.8, $P = 0.001$) and overall survival (relative risk = 4.83, 95% confidence interval = 1.1–19.9, $P = 0.029$). CONCLUSIONS: Tumor response following preoperative chemoradiation therapy is mainly related to the preoperative regimen used. For patients receiving preoperative chemoradiation therapy, pretreatment T stage, but not tumor response to preoperative chemoradiation therapy, is prognostic for outcome (both disease-free and overall survival). [Key words: Rectal cancer; Pathologic complete response; Radiotherapy; Chemotherapy; Adjuvant therapy]

Postoperative adjuvant combined chemotherapy and radiotherapy (CRT) has long been considered standard treatment for locally advanced rectal cancer (T3–T4 and or positive lymph nodes).[1] Now, however, combined preoperative CRT has gained popularity, and is accepted worldwide as a valid option in the treatment of locally advanced middle to lower rectal cancer. This approach allows high rates of tumor resectability,[2,3] sphincter-saving procedures,[4,5] and downstaging[3,6,7]; it has also been reported to improve local control and five-year survival rates.[3,6,8–10]

One potential advantage of preoperative combined treatment is that it can lead to clinical and pathologic disappearance of the tumor. Findings for pathologic complete response (pCR) after preoperative CRT vary greatly,[2,8,10–12] and predictive factors for tumor response are still a controversial issue. Most authors suggest that better outcomes may be expected for patients with a pCR after preoperative CRT.[6,13,14] However, the outcome measures (local control, or disease-free or overall survival) considered in series reported on in the literature vary.[6,13,14] Moreover, in some series no correlation has been found between pCR and outcomes.[15] A better outcome for complete responders may have relevant clinical implications, particularly in relation to the need for adjuvant treatment, and for a different surgical approach.

The aim of this study was to evaluate, in a retrospective consecutive series of locally advanced middle to lower rectal cancer, factors predictive of response to preoperative CRT and the prognostic impact of pCR on outcomes (overall survival (OS) and disease-free survival (DFS)).

PATIENTS AND METHODS

Patient Selection

Between January 1994 and June 2002, 132 consecutive patients with primary adenocarcinoma of the middle and lower rectum underwent surgery at Clinica Chirurgica II, the University of Padova, following preoperative combined CRT. The evaluation of patients included a complete clinical history and physical examination, proctoscopy and/or colonoscopy, complete blood cell count, chest x-ray, hepatic and transrectal ultrasound (TRUS), pelvic computed tomography (CT) scan, and carcinoembryonic antigen test. Criteria used for giving preoperative adjuvant-combined CRT were a) biopsy-proven adenocarcinoma of the middle and lower rectum; b) preoperative stage T3–T4 and/or node positive; c) age $\leq$75 years; and d) Eastern Cooperative Oncology Group performance status of 0 to 2. Carcinomas were considered localized in the lower two-thirds of the rectum if their lowest edge was up to 11 cm from the anal verge. To make the series more homogeneous and to rule out potential biases of patient selection, 26 patients were not included in the study for the following reasons: distant metastasis (n = 13); local residual tumor following surgery, both microscopic (n = 4) and macroscopic (n = 2); local excision (n = 4) following preoperative CRT; non-fluorouracil (5-FU)-based CRT (n = 2); or no reliable data available on the preoperative CRT regimen used (n = 1). The study group comprised the remaining 106 patients.

Chemoradiation

Preoperative therapy. Patients underwent external beam radiotherapy (RT) with LINAC (linear accelerator) x-ray (10 MV). The clinical target volume, according to the ICRU 50, included primary tumor and regional lymph nodes (mesorectal, presacral, internal iliac vessels, and obturator foramen). The four-beam "box technique" was used, with the upper border extending to L5/S1. Chemotherapy consisted of 5-FU alone or in combination with other drugs (leucovorin, carboplatin, or oxaliplatin). During the period considered, different regimens were used. Variations in preoperative therapy were related to a) the period of treatment (during the initial years of the study we routinely used 5-FU bolus together with low-dose leucovorin and external beam RT, 45 Gy in 25 fractions, and in later years we used 5-FU continuous venous infusion (CVI) and external beam RT, 50.4 Gy in 28 fractions); b) the enrollment of patients in prospective clinical trials; and c) the different treatment regimens used by the referring RT and oncological units. On the basis of preoperative CRT regimen used, patients were subdivided into two groups: 1) Regimen A: ex-

ternal beam RT (45 Gy in 25 fractions of 1.5 Gy/day) and fluorouracil (5-FU 350 mg/m^2/day) with low-dose leucovorin (10 mg/m^2/day) bolus for five days on days 1 to 5 and 29 to 33 during RT; and 2) Regimen B: external beam RT (50.4 Gy in 28 fractions of 1.8 Gy/day) and fluorouracil CVI (5-FU 225 mg/m^2/day for the duration of radiation). This regimen was used in the more recent years. Some of the patients in this second subgroup also received weekly bolus of oxaliplatin (25–60 mg/m^2/day) or carboplatin (70 mg/m^2/day) in addition to 5-FU CVI. Patients on intraveneous oxaliplatin were enrolled in Phase I–II trials in which a combination of 5-FU CVI and weekly administration of oxaliplatin were used.

Postoperative chemotherapy. Some patients were given postoperative adjuvant chemotherapy, usually four to six cycles of 5-FU 375 mg/m^2/day and leucovorin 100 mg/m^2/day, bolus on days 1 to 5 every 28 days. Again, variations in adjuvant chemotherapy administered were related to the period of treatment (during the initial years of the study we did not use adjuvant chemotherapy for patients staged as pTNM 0–I, whereas more recently adjuvant chemotherapy was given to all patients irrespective of pTNM stage); the enrollment of patients in prospective clinical trials; and the different treatment regimens used by the referring oncological units.

Surgery

Surgery was planned six to eight weeks following the completion of preoperative therapy. The inferior mesenteric artery was usually divided at its origin and standard lymphadenectomy was performed. The mesorectum was completely removed by means of a sharp dissection in the avascular planes between the fascia propria and parietal tissue under direct vision. Further technical details of total mesorectal excision (TME) are given elsewhere.[8,16]

Pathology

Surgical specimens were reviewed by two pathologists (VR, FM) who were unaware of the patients' outcome and reported findings following the American Joint Committee on Cancer TNM classification.[17] The tumor response to preoperative therapy was reported following the Tumor Regression Grade (TRG) criteria proposed by Mandard *et al.*[18] for esophageal carcinoma: TRG-1, pathologic complete response (pCR), *i.e.,* absence of viable cancer cells in the resected specimen; TRG-2, presence of residual cancer cells; TRG-3, fibrosis outgrowing residual cancer cells; TRG-4, residual cancer cells outgrowing fibrosis; and TRG-5, absence of response. The rationale for using the TRG criterion in the setting of this study was because it is a specific measure for tumor response following preoperative CRT. However, on making statistical analysis, we also considered the more standardized pTNM stage system.

Study End Points

The end points of the study were 1) the pathologic response to preoperative CRT evaluated by the TRG score; 2) tumor recurrence, defined as local (any recurrence in the pelvis) or distant (any recurrence outside the pelvis); and 3) crude OS.

Follow-Up and Statistical Analysis

Patients were examined at routine follow-up 3, 6, 12, 15, and 18 months after surgery, and then yearly. At each follow-up, carcinoembryonic antigen level was determined and liver ultrasound and sigmoidoscopy were performed. A chest x-ray and colonoscopy were performed yearly. Survival was considered the interval between surgery and the date of the last follow-up or death (OS) or the date of the last follow-up or recurrence (DFS).

Recurrence was determined by clinical examination, x-ray, or biopsy. Local recurrence was defined as a recurrence in the pelvis (tumor bed, pelvic nodes, anastomosis, drain site, or perineal scar). Any other recurrence was defined as "distant recurrence."

Continuous variables were reported as a median (range) value. The association between variables was analyzed for significance by use of Fisher's exact test or chi-squared test (for categorical variables), and the Kruskall-Wallis test (for continuous variables). Survival curves, estimated with the Kaplan-Meier method, were compared by means of the log-rank test.

To find factors predictive of tumor response following preoperative CRT, univariate and multivariate analyses were performed with logistic regression analysis and stepwise procedure. For this analysis, following the method described by Mandard *et al.*,[18] patients were subdivided into two groups: responders (TRG-1, TRG-2, TRG-3) and nonresponders (TRG-4, TRG-5).

The prognostic relevance of a single factor for OS

Table 1.
Patient Characteristics

Variable	Median (range) or No. (%)
Age (years)	60 (31–79)
Gender	
Female	40 (38%)
Male	66 (62%)
Tumor location (cm)	6 (1–11)
Preoperative cTNM stage[a]	
cT3N0	40 (38%)
cT4N0	1 (1%)
cT2N1	9 (9%)
cT3N1	37 (36%)
cT4N1	17 (16%)
Total RT dose delivered (Gy)	50.4 (40–56)
5-FU administration	
Bolus	48 (45%)
CVI	58 (55%)
CRT regimen	
A[b]	47 (44%)
B[b]	59 (56%)
Carboplatin or oxaliplatin	
Yes	71 (67%)
No	35 (33%)
Interval RT to surgery (days)	42.5 (19–136)
Surgical procedure	
Abdominoperineal resection	12 (11%)
Low anterior resection	93 (88%)
Hartmann's procedure	1 (1%)
Postoperative ChT	
Yes	59 (56%)
No	47 (44%)

Data are reported as median (range) or No. (%).ChT = chemotherapy; CRT = chemotherapy + radiotherapy; cTNM = preoperative, clinical TNM; CVI = continuous venous infusion; 5-FU = 5-fluorouracil; RT = radiotherapy.

[a]Preoperative stage available in 104 cases.

[b]Regimen A: ChT (bolus of 5-FU and leucovorin, days 1–5 and 29–33) + RT (45 Gy/25 F/1.8 Gy/F). Regimen B: ChT (5-FU CVI ± weekly bolus of carboplatin or oxaliplatin) + RT (50.4 Gy/28 F/1.8 Gy/F).

and DFS was determined by univariate analysis and Cox's multivariate proportional hazards model through stepwise procedure. A P value of ≤ 0.05 was considered statistically significant.

RESULTS

Patients, Tumor, and Treatment Characteristics

Patients, tumors, and treatment characteristics are listed in Table 1. Preoperative TNM stage was available in 104 cases, and in 9 patients, staged as cT2, regional lymph nodes were considered positive (pTNM stage III).

Pathologic response in postirradiated surgical specimens, whether reported as tumor regression grade (TRG) or as pTNM stage, is shown in Table 2.

No correlation was found between pretreatment T stage and adjuvant chemotherapy, whereas 70 and 34 patients with pretreatment N-positive and N-negative stage, respectively, underwent adjuvant chemotherapy ($P = 0.000$). Moreover, a significant percentage of patients with a higher pTNM stage or TRG score underwent postoperative chemotherapy: 42 percent of patients with pCR or pTNM stage I compared with 76 percent of those with pTNM stage 2–3 ($P = 0.004$); likewise, 63 percent of patients with poor response (TRG-4 to TRG-5) received adjuvant chemotherapy, compared to 38 percent of those with a good response (TRG-1 to TRG-2) ($P = 0.038$).

Factors Predictive of Tumor Response to Preoperative Chemotherapy and Radiotherapy

At logistic regression univariate analysis (Table 3), CVI of 5-FU (odds ratio (OR) = 0.32, 95% confidence interval (CI) = 0.14–0.73, $P = 0.007$), high RT doses delivered (OR = 0.99, CI = 0.98–0.99, $P = 0.006$), and Regimen B (OR = 0.29, CI = 0.13–0.67, $P = 0.003$) were found to be predictors of a better tumor response.

At multivariate analysis, only the CRT regimen used independently predicted a better response (Table 3).

Factors Prognostic for Disease-Free and Overall Survival

At a median follow-up of 42 (range, 1–110) months, no local recurrences and 13 distant recurrences were found. The median time interval between surgery and recurrence was 22 (range, 6–48) months. Of 19 patients with pCR, 3 had distant metastases at 16, 18, and 31 months following surgery and 3 died, 2 of them of cancer-related causes. Overall, 93 patients are alive and disease-free, 2 patients are alive with disease, and 11 patients have died, 7 of cancer-related causes. Because the number of events (recurrences and deaths) was low, and to enable statistical analyses, preoperative stage cT2 patients were considered together with cT3 stage patients, postoperative stage pT0 patients were considered together pT1 stage patients, and pT3 stage patients were considered together with pT4 stage patients.

The actuarial five-year survival was 83.6 percent for both OS and DFS.

Table 2.
Relationship Between Tumor Regression Grade and Pathologic TNM Stage Following Preoperative Chemotherapy and Radiotherapy

	pTNM Stage				
TRG[a]	pCR	1	2	3	Total
1	19	—	—	—	19 (18.3)
2	—	16	1	1	18 (17.3)
3	—	7	3	5	15 (14.4)
4	—	6	5	2	13 (12.5)
5	—	16	11	12	39 (37.5)
Total	19 (18.3)	45 (43.3)	20 (19.2)	20 (19.2)	104 (100)

pCR = pathologic complete response; TRG = tumor regression grade.
[a]TRG is reported in 104 out of 106 patients (in 2 cases, both pT3N0M0, TRG was not available).

Table 3.
Factors Associated with Tumor Response in 104 Rectal Cancer Patients[a]

	Univariate Analysis		Multivariate Analysis	
Variable	OR (CI)	*P* Value	OR (CI)	*P* Value
Age	0.98 (0.94–1.03)	NS		
Gender (male *vs.* female)	1.63 (0.73–3.62)	NS		
Tumor location	0.94 (0.81–1.10)	NS		
Pretreatment T stage (T2–T3 *vs.* T4)	1.31 (0.47–3.64)	NS		
Pretreatment N stage (–ve *vs.* +ve)	0.55 (0.24–1.25)	NS		
5-FU (bolus *vs.* CVI)	0.32 (0.14–0.73)	0.007		
Regimen (A *vs.* B)[b]	0.29 (0.13–0.67)	0.003	0.29 (0.13–0.67)	0.003
Carboplatin or oxaliplatin (yes *vs.* no)	0.77 (0.34–1.74)	NS		
Total RT dose	0.99 (0.98–0.99)	0.006		
RT to surgery interval	1.00 (0.98–1.03)	NS		

CI = confidence interval; CVI = continuous venous infusion; 5-FU = 5-fluorouracil; NS = not significant; OR = odds ratio; RT = radiotherapy; -ve = negative; +ve = positive.
[a]Data from univariate and multivariate analysis (logistic regression analysis).
[b]Regimen A: chemotherapy (bolus 5-FU and leucovorin, days 1–5 and 29–33) + RT (45 Gy/25 F/1.8 Gy/F). Regimen B: chemotherapy (5-FU CVI ± weekly bolus of carboplatin or oxaliplatin) + RT (50.4 Gy/28 F/1.8 Gy/F).

At univariate analysis, statistically significant prognostic factors for both DFS (Table 4) and OS (Table 5) were clinical pretreatment T stage and surgical procedure performed. Five-year actuarial DFS for patients with clinical pretreatment stages T2, T3, and T4 was 90 percent, 83 percent, and 41 percent, respectively ($P = 0.003$), and the corresponding five-year actuarial OS was 100 percent, 85 percent, and 43 percent, respectively ($P = 0.043$). Patients who underwent a sphincter-saving procedure had a five-year DFS and OS of 85 percent and 86 percent, respectively, compared with 63 percent and 57 percent, respectively, for patients who underwent an abdominoperineal procedure (DFS, $P = 0.021$; OS, $P = 0.023$). No statistically significant differences were found for DFS and OS on comparing the actuarial survival curves of patients with different tumor responses to preoperative treatment, whether evaluated as TRG (Fig. 1) or as pTNM stage (Fig. 2).

At multivariate analysis, the only independent prognostic factor for DFS (Table 4) and OS (Table 5) was found to be the pretreatment T stage.

DISCUSSION

This retrospective study was undertaken to identify factors predictive of tumor response following preoperative CRT and to evaluate the impact of tumor response on outcome. Our findings show that the tumor response following preoperative CRT depends on the modality of treatment used: a better tumor response is achieved with high RT doses and CVI of 5-FU. However, the outcome (DFS and OS) is unrelated to tumor response and depends on the pretreatment stage.

Clinical stage, as defined by TRUS and by CT scan with air insufflation in the rectum, is reported to be inaccurate in 10 percent to 30 percent for T stage, and

Table 4.
Factors Associated with Disease-Free Survival in 106 Rectal Cancer Patients[a]

	Univariate Analysis		Multivariate Analysis	
Variable	RR (CI)	*P* Value	RR (CI)	*P* Value
Age	0.98 (0.92–1.04)	NS		
Gender (male *vs*. female)	2.06 (0.57–7.48)	NS		
Tumor location	0.827 (0.64–1.05)	NS		
Pretreatment T stage (T2–T3 *vs*. T4)	7.13 (2.32–21.89)	0.001	7.13 (2.32–21.89)	0.001
Pretreatment N stage (+ve *vs*. –ve)	1.62 (0.52–5.03)	NS		
5-FU (bolus *vs*. CVI)	1.2 (0.38–3.7)	NS		
Regimen (A *vs*. B)[b]	1.62 (0.51–5.07)	NS		
Carboplatin or oxaliplatin (yes *vs*. no)	1.19 (0.36–3.96)	NS		
Total RT dose	1 (0.9–1.0)	NS		
RT to surgery interval	0.98 (0.9–1.0)	NS		
Postoperative ChT (yes *vs*. no)	0.69 (0.2–2.1)	NS		
SSP (yes *vs*. no)	0.29 (0.8–0.9)	0.029		
pT stage (0 *vs*. 1–2 *vs*. 3–4)		NS		
pT0 *vs*. pT1–pT2	0.54 (0.13–2.27)	NS		
pT0 *vs*. pT3–pT4	0.94 (0.22–3.96)	NS		
pN stage (+ve *vs*. –ve)	1.42 (0.3–5.1)	NS		
pTNM (0–1–2–3)		NS		
pTNM0 *vs*. pTNM1	0.53 (0.11–2.38)	NS		
pTNM0 *vs*. pTNM2	0.75 (0.15–3.76)	NS		
pTNM0 *vs*. pTNM3	0.96 (0.19–4.81)	NS		
TRG (1–2–3 *vs*. 4–5)	2.16 (0.66–7.05)	NS		

ChT = chemotherapy; CI = confidence interval; CVI = continuous venous infusion; 5-FU = 5-fluorouracil; NS = not significant; RT = radiotherapy; RR = relative risk; SSP = sphincter-saving procedure; TRG = tumor regression grade; -ve = negative; +ve = positive.

[a]Data from univariate and multivariate analysis (Cox's regression model with stepwise procedure).

[b]Regimen A: chemotherapy (bolus 5-FU and leucovorin, days 1–5 and 29–33) + RT (45 Gy/25 F/1.8 Gy/F). Regimen B: chemotherapy (5-FU CVI ± weekly bolus of carboplatin or oxaliplatin) + RT (50.4 Gy/28 F/1.8 Gy/F).

in 20 percent to 40 percent for N stage.[19–23] In our study, ultrasound T stage was evaluated following the Hildebrandt classification,[20] and pelvic CT scan was performed after air insufflation of the ampulla. Through use of this method, T1–T2 and T3 lesions are correctly identified by CT scan in 81.9 percent and 82.5 percent of cases, respectively. For N stage (considering metastatic all lymph nodes >0.5 cm of diameter), diagnostic accuracy was reported to be 79.2 percent.[22] We are aware that accuracy of clinical stage is a major concern and one of well-known disadvantages of the neoadjuvant approaches. Approaches using magnetic resonance imaging or positron emission tomography may improve accuracy of clinical stage and correctly select patient candidates for preoperative CRT.

Preoperative CRT therapy is a well-established treatment for locally advanced middle to lower rectal cancer. The absence of viable cancer cells (pCR) on the resected specimen following this treatment ranges from 4 percent to 44 percent of cases.[2,8,10–12] The reasons for this wide variability in response are unclear, and the results of studies reporting on clinicopathologic factors predictive of tumor response are controversial. Discrepancies between studies are mainly related to differences in patient selection, accuracy of preoperative staging and pathologic reports, and differences in treatments and definitions used for tumor response. Moreover, few studies take the tumor biology into account. Several biologic markers have been reported to be associated with tumor response: proliferative cellular nuclear antigen and Ki-67,[24] p27,[25] p53,[26,27] and p21 expression,[28] and apoptosis.[27] Moreover, variations in the levels of enzymes, such as thymidylate synthase, involved in the metabolism of 5-FU, may be important in predicting response to chemotherapy,[29,30] and polymorphisms of the repeated sequences in the enhancer region of the thymidylate synthase gene promoter may predict downstaging following CRT in rectal cancer.[31] Tumor biology is likely to play a key role in explaining CRT responsiveness of rectal cancer, and biologic markers should be considered in future studies in this field.

Concerning clinicopathologic factors, in two large retrospective studies on patients with locally advanced rectal cancer who underwent CRT[14] (n = 168)

Table 5.
Factors Associated with Overall Survival in 106 Rectal Cancer Patients[a]

	Univariate Analysis		Multivariate Analysis	
Variable	RR (CI)	*P* Value	RR (CI)	*P* Value
Age	1.00 (0.93–1.08)	NS		
Gender (male *vs*. female)	2.99 (0.64–13.89)	NS		
Tumor location	0.89 (0.69–1.15)	NS		
Pretreatment T stage (T2–T3 *vs*. T4)	4.83 (1.17–19.96)	0.029	4.83 (1.17–19.96)	0.029
Pretreatment N stage (+ve *vs*. –ve)	0.95 (0.26–3.49)	NS		
5-FU (bolus *vs*. CVI)	0.55 (0.11–2.78)	NS		
Regimen (A *vs*. B)[b]	0.966 (0.23–4.02)	NS		
Carboplatin or oxaliplatin (yes *vs*. no)	1.65 (0.41–6.56)	NS		
Total RT dose	0.99 (0.99–1.01	NS		
RT to surgery interval	0.98 (0.93–1.03)	NS		
Postoperative ChT (yes *vs*. no)	1.21 (0.36–1.03)	NS		
SSP (yes *vs*. no)	0.266 (0.08–0.91)	0.035		
pT stage (0 *vs*. 1–2 *vs*. 3–4)		NS		
pT0 *vs*. pT1–pT2	0.18 (0.03–1.12)	NS		
pT0 *vs*. pT3–pT4	0.85 (0.21–3.55)	NS		
PN stage (+ve *vs*. –ve)	1.86 (0.49–7.03)	NS		
pTNM (0–1–2–3)		NS		
pTNM0 *vs*. pTNM1	0.21 (0.036–1.34)	NS		
pTNM0 *vs*. pTNM2	0.58 (0.12–2.95)	NS		
pTNM0 *vs*. pTNM3	0.857 (0.17–4.28)	NS		
TRG (1–2–3 *vs*. 4–5)	1.14 (0.32–4.1)	NS		

ChT = chemotherapy; CI = confidence interval; CVI = continuous venous infusion; 5-FU = 5-fluorouracil; NS = not significant; RR = relative risk; RT = radiotherapy; SSP = sphincter-saving procedure; TRG = tumor regression grade; -ve = negative; +ve = positive.

[a]Data from univariate and multivariate analysis (Cox's regression model with stepwise procedure).

[b]Regimen A: chemotherapy (bolus 5-FU and leucovorin, days 1–5 and 29–33) + RT (45 Gy/25 F/1.8 Gy/F). Regimen B: chemotherapy (5-FU CVI± weekly bolus of carboplatin or oxaliplatin) + RT (50.4 Gy/28 F/1.8 Gy/F).

or RT alone[32] (n = 167) followed by curative surgery, Garcia-Aguilar *et al*.[14] and Berger *et al*.[32] found pCR of 13 percent and 5 percent, respectively. In neither study were clinicopathologic factors found to be associated with tumor response. Mohiuddin *et al*.[12] found an overall pCR of 30 percent. Like us, these authors observed a higher pCR rate in patients receiving 5-FU by CVI than in those receiving 5-FU bolus (67 percent *vs*. 10 percent, $P = 0.0002$), and in patients receiving total RT dose ≥55 Gy than in those receiving a radiation dose of ≤5000 Gy (44 percent *vs*. 13 percent, $P = 0.05$). Higher pCR rates have also been reported by other authors[7,11] using more aggressive CRT treatment regimens. Based on results in the literature and our findings, a routine regimen including 5-FU CVI and external beam RT of 50.4 Gy is now used at our institution. Although more aggressive treatments, including oxaliplatin or other new antineoplastic drugs added to 5-FU, have been used in Phase I–II studies, the end point of a higher pCR rate with these aggressive regimens should be weighed against an increased early and late toxicity. The main end point of the neoadjuvant treatment is improvement in DFS and OS rates. A higher pCR rate should be considered a secondary end point.

The time interval between completion of CRT and surgery may also affect the tumor response. This factor was evaluated in a French multicenter prospective study on 201 uT2–T3 rectal cancer patients. The authors[33] found that a longer time interval between completion of RT and surgery was associated with a statistically significant advantage in pCR rate: 10 percent pCR in the short-interval group (surgery performed within 2 weeks after the end of RT) *vs*. 26 percent in the longer-interval group (surgery performed 6 to 8 weeks after completion of RT) ($P = 0.007$). Because only 25 of our 106 patients underwent surgery before four weeks or after eight weeks from completion of CRT, it is not surprising that this factor was not associated with tumor response in our study.

The second aim of our study, to evaluate whether the pathologic complete response has an impact on outcome, was considered important because if pathologic response is confirmed as a prognostic factor following neoadjuvant treatment, postoperative adju-

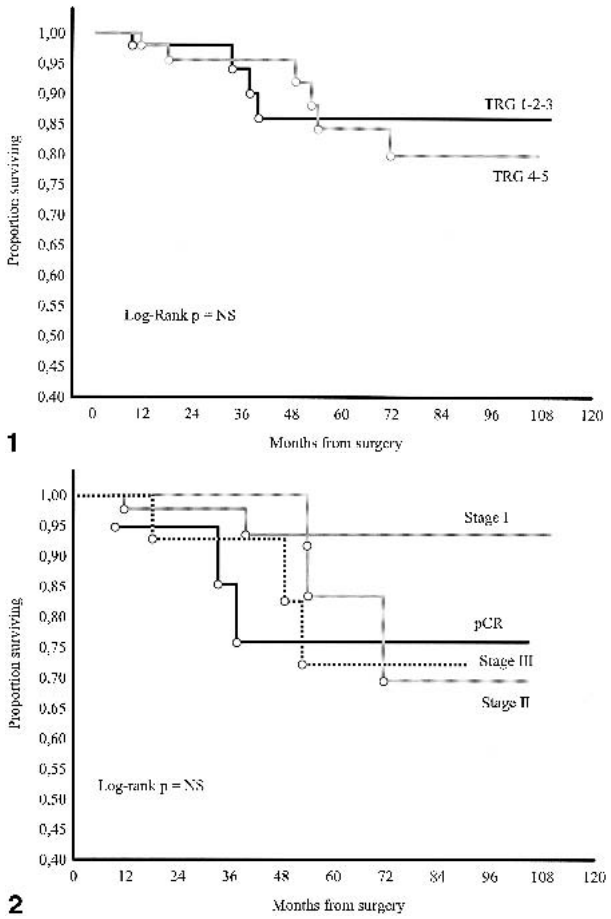

Figure 1. Overall survival curves (Kaplan-Meier) stratified by tumor regression grade in 104 patients who underwent preoperative chemoradiation therapy for middle to lower rectal cancer. NS = not significant; TRG = tumor regression grade.

Figure 2. Overall survival curves (Kaplan-Meier) stratified by pTNM stage in 106 patients who underwent preoperative chemoradiation therapy for middle to lower rectal cancer. NS = not significant; pCR = pathologic complete response.

vant treatment can be tailored on the basis of postsurgical stage rather than pretreatment stage. Moreover, a different surgical approach might be used.

Our clinical approach is now to offer routinely adjuvant chemotherapy for pretreatment of cTNM stage 2–3 rectal cancer, irrespective of the pathologic pTNM stage. The findings of our study seem to support this policy because the pretreatment T stage and not the pTNM stage was found to be a prognostic factor for outcome at multivariate analysis. Moreover, the lack of correlation between postoperative adjuvant therapy and outcome does not contradict our approach because a statistically significant percentage of patients receiving adjuvant chemotherapy had a higher pTNM stage (P = 0.004) or TRG score (P = 0.038).

On the basis of the clinical and/or pathologic complete response, some investigators advocate less invasive surgery or even a "watch-and-wait" approach.[6,34,35] Moreover, pCR may be considered a relevant end point for Phase III trials, achieved more easily and quickly than the traditional DFS and OS end points. Because no prospective studies have been conducted to investigate this aspect, it is not surprising that the retrospective series available report apparently contradictory results. Janjan *et al.*[15] found a statistically significant association between tumor size and local recurrence, but did not find that the final pathologic tumor stage affected the outcome parameters. In 22 patients with pTNM stage 0–1 of 77 patients with tethered or fixed primary and local recurrent rectal cancer who underwent preoperative radiotherapy, Mohuddin *et al.*[12] found no local or distant metastases. At multivariate analysis, the only independent factor predictive for survival was the pathologic stage. On the basis of these findings, the authors suggest that adjuvant chemotherapy be given only to pTNM stage 2–3 patients. In a report on 161 patients with locally advanced rectal cancer with a 10.5 percent pCR rate, Valentini *et al.*[6] found that pCR is correlated with OS, DFS, and freedom from distant metastasis, but not with local recurrence. However, 3 of 17 patients (18 percent) with a pCR had distant metastases. Garcia-Aguilar *et al.*[14] found in their series that female gender was the only factor associated with tumor recurrence at univariate and multivariate analysis. The estimated five-year DFS was 95 percent for patients with pCR *vs.* 55 percent for patients without a pCR (P = 0.03), but no statistically significant differences were found between patients with pTNM stages 1, 2, and 3. The authors concluded that pCR to preoperative CRT is associated with better local control and survival. In 69 T3–T4 and/or N1 patients who underwent preoperative RT with or without chemotherapy, Ruo *et al.*[36] found that recurrence-free survival was independently affected by aggressive pathologic features (angiolymphatic and/or perineural invasion) and nodal status. The marked response to preoperative treatment was associated with good long-term outcome but was not prognostic for RFS. We found that outcome is affected by the pretreatment, not pathologic, stage. Distant metastases are still an unresolved problem even for patients with a complete clinical and pathologic response. The small

number of events (local and distant recurrences, and deaths) makes statistical analysis and comparison between series questionable. To perform logistic regression analysis, TRG scores of 1, 2, and 3 were grouped together *vs.* TRG-4 and TRG-5. The main problem is how to consider TRG-3 cases (tumor with fibrosis outgrowing residual cancer cells). As suggested by Mandard *et al.*,[18] we included these patients in the "responder" group.

CONCLUSIONS

The findings reported in the present study demonstrate that in patients with locally advanced rectal cancer, the modality of 5-FU administration and the RT doses delivered affect tumor response. However, for a more reliable evaluation of factors predictive of tumor response, tumor biology and chemoresponsiveness should be taken into account.

Moreover, although our findings show that preoperative disease stage affects the outcome, studies with a greater number of events (pCR, recurrence, death), standardized treatment (both preoperative and postoperative), and adequate follow-up will lead to a better understanding of the impact of tumor response on outcome. Surgical procedure and postoperative adjuvant therapy should still be tailored on the basis of pretreatment, not pathologic, stage.

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