Importance of Tumor Regression Assessment in Predicting the Outcome in Patients with Locally Advanced Rectal Carcinoma Who Are Treated with Preoperative Radiotherapy

Hanifa Bouzourene, M.D.[1]
Fred T. Bosman, M.D., Ph.D.[1]
Walter Seelentag, M.D.[1]
Maurice Matter, M.D.[2]
Philippe Coucke, M.D.[3]

[1] Institute of Pathology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

[2] Department of Surgery, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

[3] Department of Radiation Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

Address for reprints: Hanifa Bouzourene, M.D., Institute of Pathology, 25 Rue du Bugnon, CH 1010 Lausanne, Switzerland; Fax: (011) 41-21-314-71-15; E-mail: Hanifa.Bouzourene@chuv.hospvd.ch

BACKGROUND: Locally advanced rectal carcinoma has a poor prognosis. However, since the introduction of preoperative radiotherapy, the outcome of patients with rectal carcinoma has been reported to have improved. Nevertheless, to the authors' knowledge few data are available regarding the histopathologic response to radiotherapy as assessed on surgical specimens as a potential predictive factor for outcome.

METHODS: To estimate the effect of radiotherapy on rectal carcinoma, the authors retrospectively reviewed the surgical specimens of 102 patients with T3-4, N0 or ≥ N1 rectal carcinoma and 1 patient with T2 but N1 rectal carcinoma. All patients were treated preoperatively with a hyperfractionated accelerated radiotherapy schedule in a prospective protocol (Trial 93-01). Using a standardized approach, tumor regression was graded using a system that varies from Grade 1 (tumor regression Grade [TRG] 1) when complete tumor regression is observed to Grade 5 (TRG5) when no tumor regression is observed.

RESULTS: Radiotherapy resulted in tumor downstaging in 43% of the patients. There were 2 pT1 tumors (2%), 21 pT2 tumors (20%), 66 pT3 tumors (64%), and 14 pT4 tumors (14%) after treatment. Regional lymph nodes were involved in 55 patients (53%). None of the patients demonstrated a complete tumor regression after radiotherapy, but in 79% of the specimens a partial tumor regression was observed (TRG1: 0%; TRG2: 20%; TRG3: 39%; TRG4: 20%; and TRG5: 21%). The median actuarial overall survival (OS) and disease-free survival (DFS) were 52 months. Actuarial local recurrence rates at 2 years and 5 years were 6.4% and 7.6%, respectively. Univariate analysis showed the actuarial DFS to be significantly lower in patients with lymph node metastases ($P = 0.0004$) and advanced pT stages (pT3-4) ($P = 0.03$). A favorable outcome for OS, DFS, and local control was observed in patients with TRG2-4 (i.e., responders) compared with patients with TRG5 (i.e., nonresponders), but also in patients with low residual tumor cell density (TRG2, 3, and 4). On multivariate analysis, TRG remained an independent prognostic indicator for local tumor control.

CONCLUSIONS. Tumor regression as well as residual tumor cell density were found to be predictive factors of survival in rectal carcinoma patients after preoperative radiotherapy. Even after preoperative radiotherapy, the pathologic stage of the surgical specimen remained a prognostic factor. The use of a standardized approach for pathologic evaluation must be implemented to allow comparison between the results of various treatment approaches. *Cancer* 2002;94:1121–30.
© 2002 American Cancer Society.

Colorectal carcinoma is a significant cause of morbidity and mortality in Western populations. Rectal carcinoma is characterized by a high incidence of local recurrence (20–70%), regional lymph node metastases, and distant metastases.[1,2] Major improvements have been made in the surgical control of local disease since the introduction of the so-called total mesorectal excision.[3,4] Nevertheless, the incidence of local recurrence remains high (10–30%).[5–10] Moderate- to high-dose neoadjuvant preoperative radiotherapy has been shown to induce tumor regression and downstaging, thus significantly improving local control.[7,10–18] The role of preoperative radiotherapy in survival remains controversial, with some studies reporting a minimal effect,[17,19,20] whereas in other trials a significant impact has been shown.[7–9,13,14,16,21–23] In a recent meta-analysis, it was suggested that preoperative radiotherapy significantly improves overall and cancer specific survival but much more in patients with Dukes Stage B and C tumors than in patients with Dukes Stage A tumors.[24] However, to our knowledge, the histopathologic characteristics of the response of rectal carcinoma to ionizing irradiation have been poorly documented, and the results reported from different studies often are contradictory. This can be explained by the heterogeneity in clinical staging procedures and by treatment-related factors. The lack of a standardized approach toward the pathologic assessment of tumor response certainly is another source of discrepancy.

We have developed an accelerated irradiation schedule that completes the treatment in 2.5 weeks, with the intention to counter tumor repopulation during treatment and to reduce the incidence of late complications by using hyperfractionation (i.e., reducing the dose per fraction).[25] This hyperfractionated and accelerated radiotherapy (HART) schedule immediately is followed by surgery to keep the overall treatment time as short as possible. HART has been tested in patients with locally advanced rectal carcinoma, (i.e., T3 and T4 rectal carcinomas or any T classification providing evidence of lymph node involvement) (Trial 93-01). We have demonstrated previously that preoperative HART is feasible and is associated with significantly lower toxicity compared with postoperative radiotherapy.[25,26] Based on this experience, a Phase II trial has been initiated.

The purpose of the current study was to assess the histologic response by a standardized and reproducible method and to determine its prognostic value in a series of patients with locally advanced rectal carcinoma who were prospectively treated with HART.

MATERIALS AND METHODS
Patients
This study included 103 successive patients with locally advanced rectal carcinoma (T3-4 or any T classification but N positive) who were eligible for Trial 93-01 and were treated with HART in Lausanne, Switzerland between 1992 and 1998.[25,26] The ages of the patients ranged from 28–85 years (median age, 63 years) and the gender ratio (female/male) was 1.2. Prior to the initiation of treatment, all patients underwent a rectal biopsy, complete clinical examination, blood count, assessment of renal and hepatic function, and carcinoembryonic antigen (CEA) assay. Distant metastatic disease was excluded by chest X-ray, abdominal ultrasound, and thoracoabdominal computed tomography (CT) scan. The assessment of the local extent of the tumor was based on digital rectal examination, and completed by rectal ultrasound and CT scan. In total, 102 patients were classified as having T3-4 tumors. In 27 patients (26%) we suspected lymph node involvement based on rectal ultrasound or CT findings. One patient was classified as having T2 N1 disease. All patients were irradiated with a linear accelerator with a minimal accelerating potential of 6 megavolts. The dose per fraction was 1.6 grays (Gy) and the interfraction interval was at least 6 hours. The total dose was increased to 41.6 Gy in 26 fractions given over 2.5 weeks. The interval between the end of radiotherapy and surgical resection was kept as short as possible, usually within 6 days (median of 5 days). An abdominal perineal resection was performed in 51 patients, a low anterior resection was performed in 50 patients, and an abdominal transanal resection was performed in 2 patients.

Macroscopic Examination
The surgical specimens were opened on the anterior wall and fixed in 10% buffered neutral formalin for 24 hours. The external surface of the surgical specimen was painted with permanent ink. The whole tumor and attached mesorectum were sliced serially in 3–4-mm slices and the whole tumor was included for histologic examination. For assessment of perirectal lymph nodes, adipose tissue was removed after tumor sampling and cleared in Carnoy solution over 24 hours.

Histologic Assessment
Tumor tissue blocks were embedded in paraffin, then cut and stained with hematoxylin and eosin according to standard procedure. All 103 irradiated rectal tumors were reviewed by the same pathologist (H.B.). The tumors were classified according to the World Health

Organization classification of intestinal carcinoma[27] and staged according to the TNM classification.[28] Tumor regression, degree of cytonuclear atypia, intensity of the inflammatory reaction, and the extent of necrosis were recorded. Tumor regression was graded according to a method described by Mandard et al. for the assessment of pathologic response after neoadjuvant chemoradiotherapy in esophageal carcinomas on a scale from 1–5 based on the presence of residual tumor cells and the extent of fibrosis.[29] Grade 1 is defined as the absence of residual tumor and fibrosis extending through the different layers of the rectal wall. Grade 2 is characterized by the presence of rare residual tumor cells scattered throughout the fibrosis (Fig. 1a). Grade 3 involves an increase in the number of residual cells, but the fibrosis still predominates (Fig. 1b). Grade 4 (Fig. 1c) demonstrates residual tumor outgrowing the fibrosis and Grade 5 is characterized by the absence of any tumor regression (Fig. 1d). Cytonuclear atypia were classified into mild, moderate, or marked (Fig. 2). Tumor necrosis was graded as 1 when it represented $< 25\%$ of the tumor mass, was graded as 2 when it represented 25%–50% of the tumor mass, was graded as 3 when it represented 50–75% of the tumor mass, and was graded as 4 when it represented $> 75\%$ of the tumor mass (Fig. 3). Intratumor inflammatory reaction (mononuclear and granular cells) was graded as 0 when absent or mild, 1 when moderate, and 2 when extensive.

Downstaging was determined by comparing the data regarding clinical and pathologic tumor stages.

Statistical Analysis and Follow-Up

The patients were followed for the development of local recurrence and distant metastasis every 6 months for the first 2 years and every year thereafter. A physical examination, serum CEA essay, chest X-ray, and abdominal ultrasound or CT scan were included in the follow-up procedure.

All statistical analyses were conducted using the JUMP software (SAS, Cary, NC). A P value < 0.05 was considered statistically significant. The correlation between necrosis, cytonuclear atypia, inflammatory reaction, and tumor regression grade (TRG) were stud-
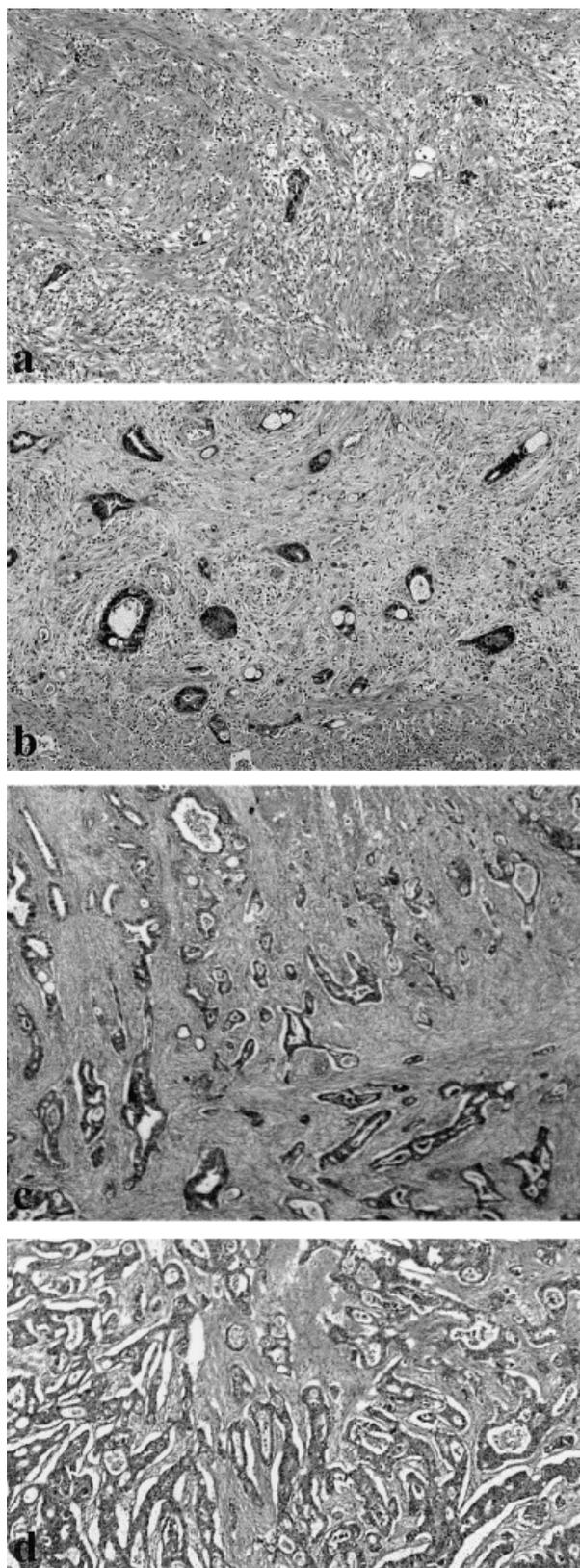

FIGURE 1. Tumor regression grading of rectal tumors in patients treated preoperatively with radiotherapy. (1a) Tumor regression Grade (TRG) 2 is characterized by the presence of rare residual tumor cells scattered through a significant fibrosis. (1b) TRG3 involves an increased number of residual cells, but the fibrosis still predominates. (1c) TRG4 demonstrates residual tumor cells outgrowing the fibrosis. (1d) TRG5 is characterized by the absence of any tumor regression.
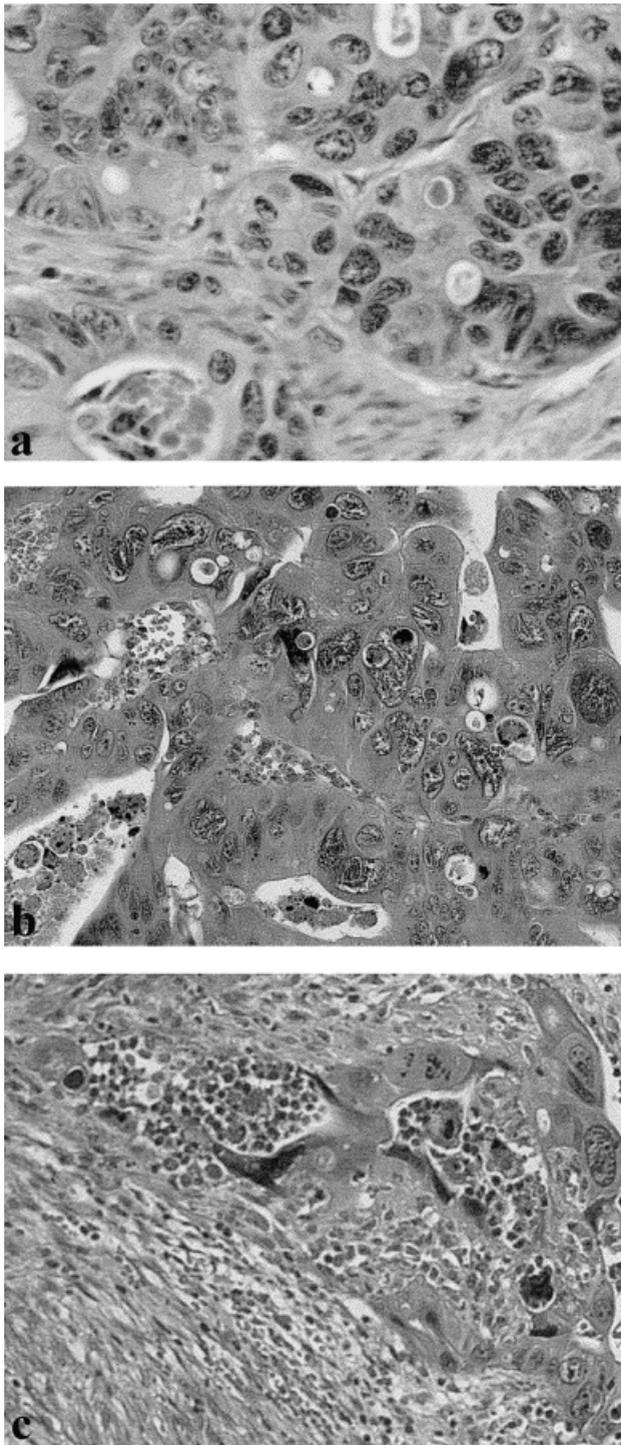
FIGURE 2. (a) Mild, (b) moderate, or (c) marked cytonuclear atypia in rectal carcinoma treated with preoperative radiotherapy.

FIGURE 3. Significant tumor necrosis involving > 75% of the tumor tissue in a rectal carcinoma from a patient treated with preoperative radiotherapy.

ied with the Pearson chi-square test. On the univariate and multivariate analyses, overall survival (OS), disease-free survival (DFS), and local control were used as the endpoints. On univariate analysis, surviv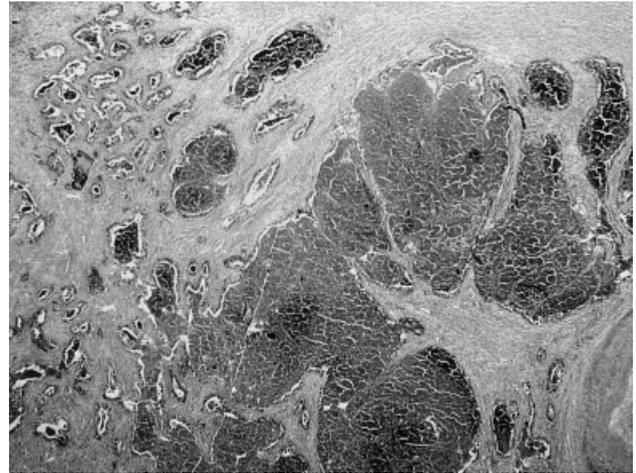al curves were estimated according to the Kaplan–Meier method for the following pathologic variables: pT classification, pN classification, tumor types, TRG, necrosis, inflammation, and cytonuclear atypia. The statistical significance of their differences was estimated using the log-rank test. To increase the number of patients per group, the categories of the various pathologic variables also were combined for theses analyses: pT1-2 versus pT3-4; well and moderately differentiated adenocarcinomas versus poorly differentiated and mucinous carcinomas; responder group (TRG2–4) versus nonresponder group (TRG5); necrosis > 25% versus necrosis < 25%; absent, mild, or moderate inflammatory reaction versus extensive inflammatory reaction; and mild or moderate cytonuclear atypia versus marked cytonuclear atypia.

The multivariate survival analysis according to the Cox proportional hazards model was constructed by backward elimination of the following variables: pT classification, pN classification, TRG, necrosis, inflammation, and cytonuclear atypia. Patient age was not included in this model because it was not found to be statistically significant on the univariate analysis.

RESULTS
Pathologic Findings
Of the 103 rectal tumors 2 were pT1 (2%), 21 were pT2 (20%), 66 were pT3 (64%), and 14 were pT4 (14%). Of all the patients, 44 (43%) had their tumor downstaged at the time of pathologic examination (Table 1). Regional lymph node metastases were found in 55 patients (53%), but there was no reported lymph node downstaging.

The histologic variables analyzed and their correlation with survival and local control are summarized

TABLE 1
Tumor Downstaging in a Series of 103 Rectal Carcinoma Patients who were Treated with Preoperative Radiotherapy

	cT2	cT3	cT4	Total
pT1	1	1	0	2 (2%)
pT2	0	19	2	21 (20%)
pT3	0	45	21	66 (64%)
pT4	0	4	9	14 (14%)
Total	1	70	32	103 (100%)

in the Table 2. Tumors were classified as well, moderately, and poorly differentiated adenocarcinoma in 25%, 40%, and 13% respectively, of the patients and the remaining 22% of patients were determined to have mucinous carcinomas. Mucinous carcinomas were found to be associated significantly with advanced pT classification (pT3-4; $P = 0.04$).

None of the 103 tumors demonstrated complete tumor regression. Partial tumor regression (TRG2-4) was noted in 79% and no regression (TRG5) was noted in 21% of the tumors. Of the tumors that did demonstrate regression, 20% were TRG2, 39% were TRG3, and 20% were TRG4. Advanced pT3-4 tumors frequently demonstrated no tumor regression (TRG5) ($P = 0.01$).

We found a strong correlation between the different levels of tumor regression and necrosis. Tumors with > 25% necrotic cells were found to have a better histologic tumor regression than tumors with < 25% necrotic cells ($P = 0.012$) (Table 3). A significant association was observed between cytonuclear atypia and tumor response, with TRG5 being highest in tumors with mild atypia and lowest in tumors with marked atypia ($P = 0.010$) (Table 3). When we analyzed the group of tumors demonstrating a partial histologic tumor regression (TRG2–4) and those without histologic tumor regression (TRG5) (Table 4), the same correlation between necrosis, cytonuclear atypia, and tumor response was observed. We also found a significant correlation between a partial tumor response and the presence of extensive inflammation ($P = 0.011$) (Table 4).

Survival Analysis

During follow-up (median, 40 months) 29 patients (28.2%) developed distant metastasis and 8 patients (7.8%) developed local recurrence. Forty-five patients died, 34 of rectal carcinoma. The median actuarial OS and DFS both were 52 months. The actuarial local recurrence rates at 2 years and 5 years were 6.4% and 7.6%, respectively. The type of surgical resection did not appear to have any influence on survival.

The influence of the various pathologic variables on survival and local control by univariate analysis is summarized in Table 2. The median actuarial OS was significantly lower in patients with lymph node metastases ($P = 0.0001$, log-rank test) and in patients with poorly differentiated or mucinous carcinoma ($P = 0.03$, log-rank test). There was a trend toward histologic response (TRG) correlating with OS ($P = 0.06$, log-rank test). When grouped together, responders (TRG2, 3, and 4) demonstrated a significantly better overall survival than nonresponders (TRG5) ($P = 0.02$, log-rank test) (Fig. 4). The median actuarial DFS was significantly lower in patients with advanced pT disease (pT3-4) ($P = 0.03$, log-rank test) and those with lymph node metastases ($P = 0.0004$, log-rank test). A significant correlation was found between the different grades of tumor response and DFS ($P = 0.04$, log-rank test) (Fig 5). The DFS was longer in responders (TRG2, 3, and 4) compared with nonresponders (TRG5) ($P = 0.03$, log-rank test). Local control appeared to be better in responders (TRG2-4) compared with nonresponders (TRG5) ($P = 0.02$, log-rank test). Tumor downstaging did not appear to correlate with survival.

Patients demonstrating more tumor necrosis tended to survive longer compared with patients who did not, but this difference did not reach statistical significance. Features such as cytonuclear atypia and inflammatory reaction did not appear to correlate with survival.

Using multivariate survival analysis we found that pT was an independent prognostic factor for OS. pT and pN were found to be independent prognostic factors for DFS whereas with regard to local control, only TRG remained an independent prognostic indicator.

DISCUSSION

Both local recurrence and distant metastasis after surgery remain major problems in the curative approach to rectal carcinoma. Preoperative radiation therapy has been shown to reduce the incidence of local recurrence and in some trials has been reported to improve survival.[7–18,22–24,30–34] Therefore, this treatment modality currently is considered part of a standard approach.[35] However, randomized trials involving preoperative radiotherapy and surgery alone are difficult to compare because there is considerable variation in the irradiation techniques between the studies. Discrepancies arising from these trials also may be due to different factors such as heterogeneity in clinical stages; the absence of a standardized method for pathologic analysis; and confusion between the pathologic stages, downstaging, and tumor regression.

TABLE 2
Univariate Analysis of Overall and Disease Free Survival and Local Control in Patients with Postirradiated Rectal Carcinoma and Histologic Variables

Variables	No.	%	OS P value	DFS P value	Local control P value
Pathologic tumor stage			0.5	0.16	0.7
pT1	2	2%			
pT2	21	20%			
pT3	66	64%			
pT4	14	14%			
Pathologic tumor stage (grouped)			0.18	0.03	0.7
Early pT (pT1 and pT2)					
Advanced pT (pT3 and pT4)					
Pathologic lymph node stage			0.0017	0.0004	0.4
pN+	55	53%			
pN0	48	47%			
Tumor differentiation			0.06	0.3	0.4
Well differentiated	26	25%			
Moderately differentiated	41	40%			
Poorly differentiated	13	13%			
Mucinous carcinoma	23	22%			
Tumor differentiation (grouped)			0.03	0.7	0.3
Well and moderately differentiated	67	65%			
Poorly differentiated and mucinous carcinoma	36	35%			
TRG			0.06	0.04	0.1
1	0	0%			
2	20	20%			
3	40	39%			
4	21	20%			
5	22	21%			
TRG (grouped)			0.02	0.03	0.02
Responder group (TRG 2, 3, and 4)	81	79%			
Nonresponder group (TRG 5)	22	21%			

OS: overall survival; DFS: disease-free survival; TRG: tumor regression grade.

TABLE 3
Correlation between Rectal Carcinoma Tumor Regression Grades 2, 3, 4, and 5 Treated Preoperatively with Radiotherapy and Tumor Necrosis, Inflammation, and Cytonuclear Atypia

	Necrosis		Inflammation			Cytonuclear atypia		
	< 25%	> 25%	Absent or mild	Moderate	Extensive	Mild	Moderate	Marked
TRG	P = 0.012		P = 0.131			P = 0.010		
TRG2	20%	17%	15%	23%	15%	10%	18%	22%
TRG3	27%	58%	27%	46%	39%	30%	32%	45%
TRG4	25%	17%	22%	22%	23%	0%	23%	25%
TRG5	28%	8%	36%	9%	23%	60%	27%	8%

TRG: tumor regression grade.

To our knowledge to date, very few studies regarding the histologic manifestations of tumor response to preoperative radiotherapy have been reported and few provide a detailed analysis of tumor regression. The extent of the histologic response to preoperative radiotherapy varies from tumor to tumor, with some being more radioresponsive than others. Therefore, a systematic pathologic workup is essential if one wishes to compare the results of preoperative radiotherapy between different groups.

We have reported previously that preoperative HART, an innovative schedule of radiotherapy for patients with rectal carcinoma, is feasible, improves the radical resection rate, and induces a significantly

TABLE 4
Correlation between Tumor Responders versus Nontumor Responders and Necrosis, Inflammation, and Cytonuclear Atypias

| | Necrosis | | Inflammation | | | Cytonuclear atypias | | |
| | P = 0.022 | | P = 0.011 | | | P = 0.000 | | |
TRG	< 25%	> 25%	Absent	Moderate	Extensive	Mild	Moderate	Marked
PR (TRG2-4)	72%	92%	64%	91%	77%	40%	73%	92%
NR (TRG5)	28%	8%	36%	9%	23%	60%	27%	8%

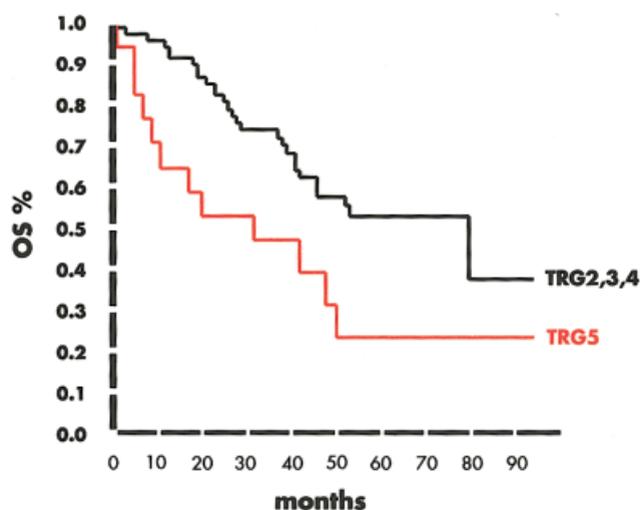TRG: tumor regression grade; PR: partial response; NR: no response.

FIGURE 4. Overall survival (OS) in the responder group (tumor regression Grades [TRG] 2, 3, and 4) was better than in the nonresponder group (TRG 5) (P = 0.02, log-rank test).
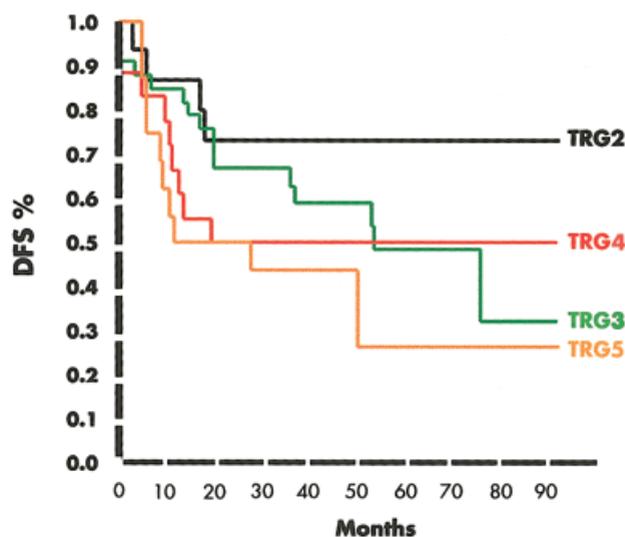

FIGURE 5. A significant correlation was observed between tumor regression grade (TRG) and disease-free survival (DFS) in patients with rectal carcinoma who were treated with preoperative radiotherapy (P = 0.03, log-rank test).

lower acute toxicity compared with postoperative radiotherapy.[25,26] Our current prospective series includes only patients with locally advanced rectal carcinoma who were treated with the same schedule of preoperative HART. The objective of the current study was to evaluate the histologic manifestations of tumor response and its correlation with OS, DFS, and local control. Using a standardized method, we analyzed specifically tumor regression and histologic parameters such as necrosis, inflammatory reaction, and cytonuclear atypia that can influence tumor regression.

One of the first simple and reproducible grading systems for tumor regression was described by Mandard et al. in patients with esophageal carcinoma who were treated preoperatively by chemoradiotherapy.[29] More recently, Dworak et al. proposed a tumor regression grading system for rectal carcinoma (Grade 0 for no tumor regression, Grade 1 for dominant tumor, and Grade 3 for tumor with few cells) and demonstrated that 16 of 17 patients treated with preoperative chemoradiotherapy achieved a significant response,

but no patient achieved complete regression of tumor.[36] Using the tumor regression grade elaborated by Mandard et al., Bozzetti et al. reported a > 50% response (TRG1, 2, and 3) in 13 of 20 patients undergoing preoperative radiotherapy for rectal carcinoma, with 1 patient achieving complete regression.[37] In the current series, we also used the grading system of Mandard et al. for tumor regression and observed that 79% of the patients achieved a partial tumor regression and that 21% of patients demonstrated no evidence of tumor regression. In contrast to some studies, we did not observe a single case of complete tumor regression in patients with rectal carcinoma after preoperative radiotherapy.[7,30,38] This might be explained by the short delay between the end of the radiotherapy and surgery in the schedule used in the current study and also by the fact that only patients with locally advanced stages of rectal carcinoma were included in the current study compared with other studies in which a significant proportion of patients

with cT1-T2 tumors was included.[30] To our knowledge, there have been no reports to date of complete tumor regression occurring when surgery is performed within 1 week after the end of radiotherapy, a finding that is consistent with our own data.[10,12,14,16,17,19] In contrast, in studies with a longer interval between the end of radiotherapy and surgery (> 10 days), complete histologic regression was reported in 2–11% of the patients.[7,30,38–41] However, to diagnose complete tumor regression, the entire tumor region must be sampled and carefully screened for any small surviving foci of carcinoma by thorough histologic workup.

Results regarding a possible correlation between survival and tumor regression are contradictory. The results of the current study indicate that the responders (TRG2–4) have better OS, DFS, and local control than nonresponders (TRG5). Moreover, residual tumor cell density was found to be correlated highly with DFS; however, it remains an independent prognostic indicator only for local control. Some pathologic parameters such as necrosis, degree of cytonuclear atypia, and inflammation were, as one could expect, found to be related closely to TRG and therefore were not considered to be independent and were not determined to be correlated significantly with outcome on multivariate analysis. Berger et al. found that OS and DFS rates for patients with a complete histologic response are better but that residual tumor cell density is not a prognostic factor.[30] Kaminsky-Forrett et al. demonstrated that patients with significant tumor regression, (i.e., no residual tumor cells or only rare foci of residual cells localized in the submucosa and/or invaded muscularis propria) have a significantly higher cancer specific survival rate compared with patients without tumor regression.[39]

We found, both in the current series and in accordance with the literature,[30,32,33,39] that prognosis remained dependent on pN status for OS, and pT and pN status for DFS, even after radiotherapy.

Tumor downstaging has been regarded as a marker for tumor radiosensitivity and has been reported to be an important prognostic factor.[30,39,42] However, a recent review of randomized trials of preoperative radiotherapy versus surgery alone demonstrated that very few available objective and controlled data (i.e., after pathologic review) concerning downstaging rates were available.[43] In the current series, we observed a very high rate of downstaging (43%) but the OS and DFS in patients whose tumors were downstaged after preoperative radiotherapy did not appear to improve compared with patients whose tumors were not downstaged. The discrepancies between the current study results and those from previous studies may be due to the absence of a clear definition of tumor downstaging and a frequent confusion of it with TRG. In fact, in the current series, there was not an apparently perfect correlation between tumor downstaging and tumor regression, because several tumors remained at the same pathologic stage after radiotherapy even if the tumor cell density significantly decreased and necrosis increased.

Results concerning lymph node downstaging also are variable in the literature. In the current series, we found no downstaging of lymph node metastases after preoperative radiotherapy. In contrast, we observed a higher incidence of positive lymph nodes on pathologic examination than was yielded by clinical N classification (53% vs. 27%). However, we believe this finding merely indicates the lack of reliability of preoperative staging by radiologic techniques. Moreover, our method of lymph node dissection by clearing mesorectal fat significantly facilitated the detection of lymph node metastases. In the literature data, a reduced number of lymph node metastases after preoperative radiotherapy was reported in some studies[8,16,18,38,42,44] whereas in other studies no significant difference was found.[12,17,32]

CONCLUSIONS

Based on this comprehensive pathologic review of 103 surgical specimens of locally advanced rectal tumors after preoperative HART, we conclude that there is a strong correlation between TRG and outcome. We tentatively raise the hypothesis that TRG can be used to stratify patients in trials, raising questions regarding the need for postoperative adjuvant treatment.

REFERENCES

1. Bosset JF, Arbez-Gindre F, Pelissier E, Mantion G, Camelot G, Gillet M, et al. Facteurs anatomo-pathologiques de pronostic des cancers du rectum. Etude mono- et multifactorielle. *Gastroenterol Clin Biol* 1986;10:728–35.
2. Minsky BD, Mies C, Recht A, Rich T, Chaffey J. Resectable adenocarcinoma of the rectosigmoid and rectum. Patterns of cancer failure and survival. *Cancer* 1988;61:1408–16.
3. Adam IJ, Mohamdee MO, Martin IG, Scott N, Finan PJ, Johnston D, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet* 1994;344:707–11.
4. Quirke P, Durdey P, Dixon MF, Rich T, Chaffey J. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet* 1986;1:996–8.
5. Balslev I, Pedersen M, Teglbjaerg PS, Hanberg-Soerensen F, Bone J, Jacobsen NO, et al. Postoperative radiotherapy in Dukes' B and C carcinoma of the rectum and rectosigmoid. A randomized multicenter study. *Cancer* 1986;58:22–8.
6. Duncan W. Adjuvant radiotherapy in rectal cancer: the MRC trials. *Br J Surg* 1985;72(Suppl):S59–62.

7. Gerard A, Buyse M, Nordlinger B, Loygue J, Pene F, Kempf P, et al. Preoperative radiotherapy as adjuvant treatment in rectal cancer. Final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). *Ann Surg* 1988;208:606–14.

8. Horn A, Morild I, Dahl O. Tumour shrinkage and downstaging after preoperative radiation of rectal adenocarcinoma. *Radiother Oncol* 1990;18:19–28.

9. Rider WD, Palmer JA, Mahoney LJ, Robertson CT. Preoperative irradiation in operable cancer of the rectum: report of the Toronto trial. *Can J Surg* 1977;20:335–8.

10. Stockholm Colorectal Cancer Study Group. Preoperative short-term radiation therapy in operable rectal carcinoma. A prospective randomized trial. *Cancer* 1990;66: 49–55.

11. Glimelius B, Isacsson U, Jung B, Pahlam L. Radiotherapy in addition to radical surgery in rectal cancer-evidence for a dose-response effect favouring preoperative treatment. *Int J Radiat Oncol Biol Phys* 1997;15:281–7.

12. Goldberg PA, Nicholls RJ, Porter NH, Love S, Grimsey JE. Long term results of a randomized trial of short-course low dose adjuvant preoperative radiotherapy for rectal cancer: reduction in local treatment failure. *Eur J Cancer* 1994;30A: 1602–6.

13. Reis Neto JA, Quilici FA, Reis JA. A comparison of nonoperative vs. preoperative radiotherapy in rectal carcinoma. A 10-year randomized trial. *Dis Colon Rectum* 1989;32:702–10.

14. Stockholm Colorectal Cancer Study Group. Randomized study on preoperative radiotherapy in rectal carcinoma. *Ann Surg Oncol* 1996;3:423–30.

15. Swedish Rectal Cancer Trial. Local recurrence rate in a randomized multicenter trial of preoperative radiotherapy compared with operation alone in resectable rectal carcinoma. *Eur J Surg* 1996;162:397–402.

16. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997;336:980–7.

17. Marsh PJ, James RD, Shofield PF. Adjuvant preoperative radiotherapy for locally advanced rectal carcinoma. Results of a prospective randomized trial. *Dis Colon Rectum* 1994; 37:1205–14.

18. Medical Research Council Rectal Cancer Working Party. Randomised trial of surgery alone versus radiotherapy followed by surgery for potentially operable locally advanced rectal cancer. *Lancet* 1996;348:1605–10.

19. Higgins GA, Humphrey EW, Dwight RW, Roswit B, Lee LE Jr., Keehn RJ. Preoperative radiation and surgery for cancer of the rectum. Veterans Administration Surgical Oncology Group Trial II. *Cancer* 1986;58:352–9.

20. Second Report of an MRC Working Party. The evaluation of low dose pre-operative X-ray therapy in the management of operable rectal cancer: results of a randomly controlled trial. *Br J Surg* 1984;71:21–5.

21. Coia LR, Gunderson LL, Haller D, Hoffman J, Mohiuddin M, Tepper JE, et al. Outcomes of patients receiving radiation for carcinoma of the rectum. Results of the 1988-1989 patterns of care study. *Cancer* 1999;86:1952–8.

22. Reed WP, Garb JL, Stark AJ, Chabot JR, Friedmann P. 10-year results of preoperative radiotherapy in treatment of rectal carcinoma. *Chirurg* 1996;67:621–4.

23. Roswit B, Higgins GA, Keehn RJ. Preoperative irradiation for carcinoma of the rectum and rectosigmoid colon: report of a National Veterans Administration randomized study. *Cancer* 1975;35:1597–602.

24. Camma C, Giunta M, Fiorica F, Pagliaro L, Craxi A, Cottone M. Preoperative radiotherapy for resectable rectal cancer: a meta-analysis. *JAMA* 2000;284:1008–15.

25. Coucke PA, Sartorelli B, Cuttat JF, Jeanneret W, Gillet M, Mirimanoff RO, et al. The rationale to switch from postoperative hyperfractionated accelerated radiotherapy to preoperative hyperfractionated accelerated radiotherapy in rectal cancer. *Int J Radiat Oncol Biol Phys* 1995;32: 181–8.

26. Coucke PA. On behalf of the participants to Trial 93-01: curative resection rate after Hyperfractionated Accelerated Radiotherapy (HART) immediately followed by surgery in locally advanced rectal cancer. *Radiother Oncol* 1997; 43(Suppl 2):S45.

27. World Health Organization. International histological classification of tumors. Histological typing of intestinal tumours. 2nd edition. Berlin: Springer-Verlag, 1989.

28. Sobin LH, Wittekind Ch., editors. International Union Against Cancer. TNM classification of malignant tumours. 5th edition. New York: John Wiley & Sons, Inc., 1997.

29. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer* 1994;73:2680–6.

30. Berger C, de Muret A, Garaud P, Chapet S, Bourlier P, Reynaud-Bougnoux A, et al. Preoperative radiotherapy (RT) for rectal cancer: predictive factors of tumor downstaging and residual tumor cell density (RTCD): prognostic implications. *Int J Radiat Oncol Biol Phys* 1997;37:619–27.

31. Pahlam L, Glimelius B. The value of adjuvant radio (chemo) therapy for rectal cancer. *Eur J Cancer* 1995;31A:1347–50.

32. Gerard JP, Chapet O, Morignat E, Romestaing P, Mornex F, Acharki A. Preoperative radiotherapy of rectal cancer. The Lyon experience 1985-1996. Prognostic study a propos of 312 patients. *Ann Chir* 1999;53:1003–10.

33. Luna-Perez P, Trejo-Valdivia B, Labastida S, Garcia-Alvarado S, Rodriguez DF, Delgado S. Prognostic factors in patients with locally advanced rectal adenocarcinoma treated with preoperative radiotherapy and surgery. *World J Surg* 1999;23:1069–74.

34. Petersen S, Hellmich G, Baumann M, et al. Brief preoperative radiotherapy in surgical therapy of rectal carcinoma. Long term outcome of a prospective randomized study. *Chirurg* 1998;69:759–65.

35. NIH Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. *JAMA* 1990;19:1444–50.

36. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. *Int J Colorectal Dis* 1997;12:19–23.

37. Bozzetti, F, Andreola, S, Rossetti C, Zucali R, Meroni E, Baratti D, et al. Preoperative radiotherapy for resectable cancer of the middle-distal rectum: its effect on the primary lesion as determined by endorectal ultrasound using flexible echo colonoscope. *Int J Colorectal Dis* 1996; 11:283–6.

38. Dahl O, Horn A, Morild I, Halvorsen JF, Odland G, Reinertsen S, et al. Low-dose preoperative radiation postpones recurrences in operable rectal cancer. Results of a randomized multicenter trial in Western Norway. *Cancer* 1990;66: 2286–94.

39. Kaminsky-Forrett MC, Conroy T, Luporsi E, Peiffert D, La-peyre M, Boissel P, et al. Prognostic implication of down-staging following preoperative radiation for operable T3-T4 rectal cancer. *Int J Radiat Oncol Biol Phys* 1998;42:935–41.
40. Mendenhall WM, Bland EM, Copeland EM, Summers GE, Pfaff WW, Souba WW, et al. Does preoperative radiation therapy enhance the probability to local control and survival in high risk distal cancer? *Ann Surg* 1992;215:696–705.
41. Mohiuddin M, Marks G. High dose preoperative irradiation for cancer of the rectum. *Int J Radiat Oncol Biol Phys* 1991; 20:37–43.
42. Graf W, Dahlberg M, Osman MM, Homberg L, Pahlam L, Grimelius B. Short-term preoperative radiotherapy results in down-staging of rectal cancer: a study of 1316 patients. *Radiother Oncol* 1997;43(2):133–7.
43. Wheeler JM, Warren BF, Jones AC, Mortensen NJ. Preoperative radiotherapy for rectal cancer: implications for surgeons, pathologists and radiologists. *Br J Surg* 1999;86:1108–20.
44. Ahmad NR, Nagle D. Long-term results of preoperative radiation therapy alone for stage T3 and T4 rectal cancer. *Br J Surg* 1997;84:1445–8.