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Prognostic Significance of Tumor Regression After Preoperative Chemoradiotherapy for Rectal Cancer

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ABSTRACT

Purpose
We assessed the impact of tumor regression grading (TRG) and its value in correlation to established prognostic factors in a cohort of rectal carcinoma patients treated by preoperative chemoradiotherapy (CRT).

Patients and Methods
TRG was evaluated on surgical specimens of 385 patients treated within the preoperative CRT arm of the CAO/ARO/AIO-94 trial: 50.4 Gy was delivered, fluorouracil was given in the first and fifth week, and surgery was performed 6 weeks thereafter. TRG was determined by the amount of viable tumor versus fibrosis, ranging from TRG 4 when no viable tumor cells were detected, to TRG 0 when fibrosis was completely absent. TRG 3 was defined as regression more than 50% with fibrosis outgrowing the tumor mass, TRG 2 was defined as regression less than 50%, and TRG 1 was defined basically as a morphologically unaltered tumor mass. We performed an initially unplanned, hypothesis-generating analysis with respect to the prognostic value of this TRG system.

Results
TRG 4, 3, 2, 1, 0 was found in 10.4%, 52.2%, 13.8%, 15.3%, and 8.3% of the resected specimens, respectively. Five-year disease-free survival (DFS) after CRT and curative resection was 86% for TRG 4, 75% for grouped TRG 2 + 3, and 63% for grouped TRG 0 + 1 ($P = .006$). On multivariate analysis, the pathologic T category and the nodal status after CRT were the most important independent prognostic factors for DFS.

Conclusion
In this exploratory analysis, complete (TRG 4) and intermediate pathologic response (TRG 2 + 3) suggested improved DFS after preoperative CRT. TRG assessment should be implemented in pathologic evaluation and prospectively validated in further studies.

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INTRODUCTION

After curative surgery, tumor extension through the rectal wall and spread to the regional lymph nodes are the main criteria to estimate prognosis in rectal carcinoma patients. In locally advanced disease, postoperative chemoradiotherapy (CRT) has been shown to improve local control and survival when compared with surgery alone.[1,2] A recently published trial from our group demonstrated that preoperative CRT is superior to postoperative treatment in terms of local control and toxicity.[3] Given these advantages, preoperative CRT has been used increasingly in the management of this group of patients in recent years.

Radiotherapy and chemotherapy, if applied before surgery, may alter the pathologic T and N categories. This is achieved by reducing the depth of tumor invasion and, in a varying percentage, by causing even complete disappearance of the malignant cells in the rectal wall and in perirectal

nodes. Such downstaging effects—as documented by a decrease of pathologic versus preoperative clinical T/N categories—have been used to measure tumor response.[4-6] Preoperative staging techniques, however, such as endorectal ultrasound (ERUS), computed tomography (CT) scans, or magnetic resonance imaging scans, are limited in their ability to provide accurate information on the T and N categories.[7] Thus, assessment of response comparing the preoperative ERUS stage with the pathology stage probably overestimates the rate of tumor downstaging caused by preoperative CRT.

An alternative method to assess treatment response is accomplished by grading histologic changes in the resected specimen that are caused by preoperative CRT. These changes include cytologic alteration such as cytoplasmic vacuolation and nuclear pleomorphism, as well as stromal changes such as fibrosis with mucin pools at the site of previous tumor.[8-10] Areas of fibrotic changes after preoperative CRT contrast sharply with residual tumor and the adjacent normal bowel wall. Thus, tumor regression can range from no evidence of any treatment effect to a complete response with no viable tumor identified. Whether the extent of tumor regression has a significant impact on prognosis is an issue to be clarified.

The pathology recording of our CAO/ARO/AIO-94 trial included a prospective assessment of tumor response to neoadjuvant CRT using a standardized 5-point tumor regression grading (TRG), as initially described by Dworak et al.[8] For the analysis presented here, we performed an initially unplanned, exploratory, hypothesis-generating analysis with respect to the prognostic value of this TRG system. We present the results after a median follow-up time of 41 months.

PATIENTS AND METHODS

Eligibility

Patients were enrolled between February 1995 and September 2002. Eligibility criteria included histologically confirmed adenocarcinoma, signet ring carcinoma, mucinous carcinoma, or undifferentiated carcinoma (WHO classification) with the inferior margin within 16 cm from the anal verge. ERUS and a CT scan of the abdomen were performed to exclude TNM stage I and IV tumors.[11] Patients were excluded if they were older than 75 years, had previously had cancer other than nonmelanoma skin cancer, had previously received chemotherapy or radiotherapy, or had contraindications to CRT. The trial was approved by the medical ethics committees of all participating hospitals.

Treatment Plan

Patients were randomly assigned to preoperative or postoperative CRT. Preoperative radiotherapy consisted of 50.4 Gy, delivered in 28 fractions, to the true pelvis with individually shaped portals. Radiation techniques have been described in more detail elsewhere.[3,12] During the first and fifth weeks of radiotherapy, fluorouracil was administered as a 120-hour continuous infusion at a dose of 1,000 mg/m^2/d. Surgery was scheduled 6 weeks after completion of CRT. Techniques of surgery were standardized using total mesorectal excision; however, a quality assurance of surgery by the pathologist was not implemented. Four cycles of bolus fluorouracil (500 mg/m^2/d five times weekly, repeated every 4 weeks) were started 4 weeks after surgery.

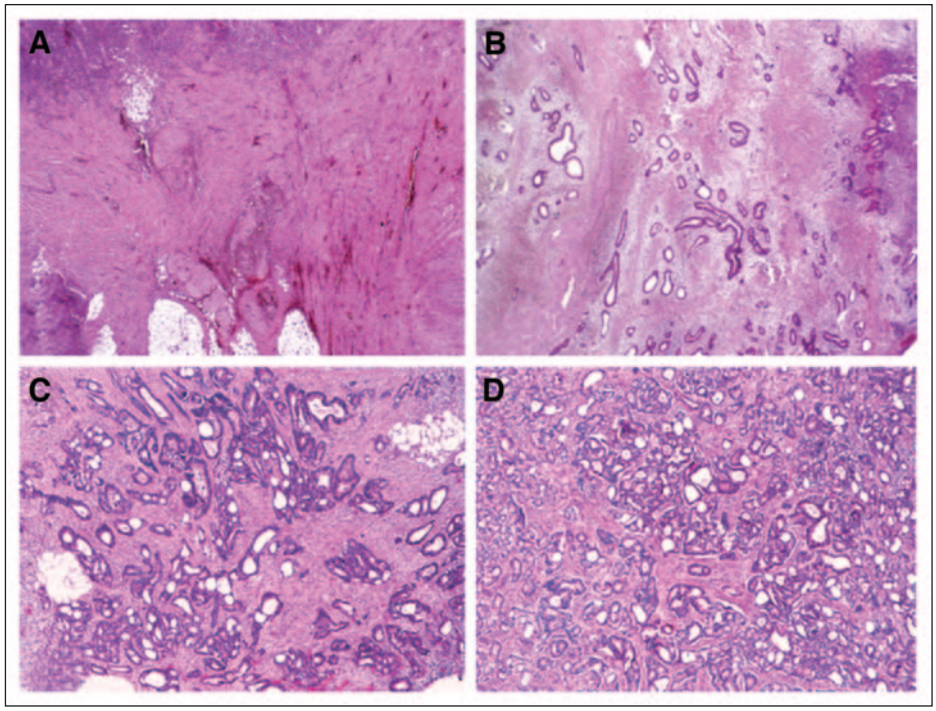

Fig 1. Tumor regression grading (TRG) after preoperative chemoradiotherapy in rectal cancer patients: (A) total regression, no viable tumor cells, only fibrotic mass, TRG 4; (B) dominant fibrosis outgrowing the tumor mass (ie, more than 50% tumor regression), TRG 3; (C) dominant tumor mass with obvious fibrosis in 26% to 50% of the tumor mass, TRG 2; (D) minor regression, fibrosis in only 25% or less of the tumor mass, TRG 1.

Table 1. TRG With Respect to Primary Tumor in 385 Patients Treated With Preoperative Chemoradiotherapy and Surgery

TRG	Patients	
	No.	%
0 (no regression)	32	8.3
1 (< 25% of tumor mass)	59	15.3
2 (≥ 25%-50% of tumor mass)	53	13.8
3 (> 50% of tumor mass)	201	52.2
4 (complete regression)	40	10.4

Abbreviation: TRG, tumor regression grading.

Pathology and TRG

All resection specimens were examined by the local pathologists from 26 participating hospitals according to a standardized protocol that included TNM categories; stage grouping; number of examined/involved lymph nodes; tumor differentiation; and status of oral, aboral, and circumferential resection margins. R0 was defined as histologically tumor-free resection margins regardless of the distance between tumor and resection margins.[11] The tissue sections were also evaluated for the presence of lymphatic and venous invasion. Data were recorded on a standardized documentation sheet that was tested for plausibility in each patient by a reference pathologist (C.W.). All pathologists were blinded to the patients' clinical outcome. A central pathology review for TRG was not performed.

The resected specimen were fixed in 4% formaldehyde overnight. After it was opened, the tumorous or fibrotic area was identified and described macroscopically. For obvious residual primary tumor, it was recommended that a minimum of four paraffin blocks be processed. If no tumor was visible, the whole (mostly fibrotic) area suggestive of disease was sliced (5- to 8-μm-thick slices) and embedded. The median and mean number of blocks examined was 5 and 6.43, respectively (range, one to 60). Tumor regression of the primary tumor was semiquantitatively determined by the amount of viable tumor versus the amount of fibrosis, ranging from no evidence of any treatment effect to a complete response with no viable tumor identified, as described by Dworak et al (Fig 1).[8] The following were characteristics of each grade: grade 0, no regression; grade 1, minor regression (dominant tumor mass with obvious fibrosis in 25% or less of the tumor mass); grade 2, moderate regression (dominant tumor mass with obvious fibrosis in 26% to 50% of the tumor mass); grade 3, good regression (dominant fibrosis outgrowing the tumor mass; ie, more than 50% tumor regression); and grade 4, total regression (no viable tumor cells, only fibrotic mass).

Follow-Up

Follow-up occurred at 3-month intervals for 2 years, then at 6-month intervals for 3 years. Evaluations consisted of physical examination and blood tests. Proctoscopy, abdominal ultrasound, CT of the abdomen, and chest radiography were also applied according to guidelines of the German Cancer Society.[13] Histologic confirmation of local and distant recurrence was encouraged. Alternate acceptable criteria included sequential enlargement of a mass in radiologic studies.

Statistical Analysis

The χ^2 trend test for ordered categories was used for ordered prognostic factors with more than two categories. No pairwise comparisons were made; only overall tests were performed. These tests took into account the ordinal character of the covariates. For dichotomous variables, the ordinary χ^2 test was used.

Disease-free survival (DFS) after curative (R0) surgery as well as local relapse-free and metastases-free survival were measured from the time of random assignment. Data from patients who where alive and free of recurrence or died without recurrence were censored for the analysis of DFS and recurrences. Univariate analyses of survival were carried out by the Kaplan-Meier method, and the evaluation of differences was performed with the log-rank test for trend with equally spaced metric for ordered prognostic factors with more than two categories. For dichotomous variables, the ordinary log-rank test was used. The multivariate survival analysis was performed according to the Cox proportional hazards model

Table 2. Association of TRG With Pretreatment Patients and Tumor Characteristics in 385 Patients Receiving Preoperative Chemoradiotherapy

Characteristic	TRG 0 + 1		TRG 2 + 3		TRG 4		Total		*P*
	No.	%	No.	%	No.	%	No.	%	
Age, years									
≤ 61	49	24.3	130	64.4	23	11.4	202	100	.89
> 61	42	23	124	67.8	17	9.3	183	100	
Sex									
Male	68	24.3	186	66.4	26	9.3	280	100	.32
Female	23	21.9	68	64.8	14	13.3	105	100	
Clinical T category									
cT2	5	31.2	7	43.8	4	25	16	100	.18
cT3	63	23.6	178	66.4	27	10.1	268	100	
cT4	7	29.2	17	70.8	0	0	24	100	
Unknown	16	20.8	52	67.6	9	11.7	77	100	
Clinical N category									
N0	38	24.7	98	63.6	18	11.7	154	100	.90
N+	46	21.6	147	69	20	9.4	213	100	
Unknown	7	38.9	9	50	2	11	18	100	

Abbreviation: TRG, tumor regression grading.

Table 3. Association of TRG With Pathologic Factors After Preoperative CRT and Surgical Resection (n = 385)

Characteristic	TRG 0 + 1 (n = 91)		TRG 2 + 3 (n = 254)		TRG 4 (n = 40)		P
	No.	%	No.	%	No.	%	
ypT category							
T0	0		0		40	100	.03*
T1	4	4.4	18	7.1	NA		
T2	23	25.3	92	36.2	NA		
T3	58	63.7	136	53.5	NA		
T4	5	5.5	8	3.1	NA		
Unknown	1	1.1	0		NA		
ypN category							
N0	53	58.2	173	68.1	36	90	.001
N+	37	40.7	81	31.9	4	10	
Unknown	1	1.1	0		0		
UICC TNM stage							
No tumor	0		0		36	90	< .001
I	20	22	85	33.5	0		
II	32	35.2	81	31.9	0		
III	31	34.1	68	26.8	4	10	
IV	8	8.8	20	7.8	0		
Grading							
No tumor	0		0		40	100	.24*
1/2	72	79.1	203	80	NA		
3/4	19	20.9	37	14.6	NA		
Unknown	0		14	5.5	NA		
Lymphatic invasion							
L0	65	71	193	76	40	100	.39*
L1	24	26	56	22	NA		
Unknown	2	2	5	2	NA		
Venous invasion							
V0	81	89	244	96	40	100	.03*
V1	9	10	10	4	NA		
Unknown	1	1	0		NA		
Interval completion of CRT to surgery							
≤ Median (35 days)	45	49.5	148	58.3	19	47.5	.69
> Median	46	50.5	104	41	21	52.5	
Unknown	0		2	0.7	0		
Completeness of local resection							
R0	84	92	250	98	40	100	.012
R1	3	3	1	0.4	0		
R2	2	2	1	0.4	0		
Unknown	2	2	2	0.8	0		

Abbreviations: TRG, tumor regression grading; NA, not applicable; CRT, chemoradiotherapy; UICC, International Union Against Cancer.
*Statistical analysis was restricted to TRG 0 + 1 *v* TRG 2 + 3 for these variables, as no detectable primary tumor (ie, TRG 4) corresponds to ypT0, and grading, lymphatic, and venous invasion are NA for TRG 4.

by backward elimination of factors found to be statistically significant on the univariate analyses. All *P* values refer to the Wald test of Cox proportional hazards regression. Ordered categoric variables were coded as continuous variables analogously to the log-rank trend test. A two-sided *P* value of less than .05 was considered significant.

No adjustment for multiple testing was performed with respect to the number of potential prognostic factors (10) or the number of outcomes (three) analyzed. Thus, *P* values are not strictly confirmative, and the analyses are considered exploratory and hypothesis generating. Moreover, grouping of the 5-point TRG was done to avoid small categories. For the analysis presented here, we used three groups (complete regression, TRG 4; intermediate regression, TRG 2 + 3; and poor regression, TRG 0 + 1). Different groupings would have led to weaker results.

RESULTS

Patients

Of 823 patients recruited, 421 were randomly assigned to preoperative CRT; 16 patients not meeting the inclusion criteria were excluded from the analysis. Nine patients requested a change to the postoperative group. Given that 19 patients allocated to postoperative CRT requested a change

to preoperative CRT, a total of 415 patients received preoperative CRT; 411 patients underwent surgery. An assessment of TRG was available in 385 patients, and in 348 of these a curative surgery was accomplished. Four of these 348 patients were lost to follow-up, leaving a total of 344 patients for evaluation of DFS.

TRG and Association With Pretreatment and Postoperative Clinicopathologic Factors

Of the 385 tumors examined for TRG, 10.4% showed no viable tumor cells in the rectal wall (TRG 4), whereas 8.3% demonstrated no regressive changes (Table 1). Overall, none of the pretreatment factors significantly predicted TRG (Table 2). A complete pathologic regression of the primary tumor (TRG 4) was seen in 25% of uT2, 10.1% of uT3, and in none of the uT4 tumors.

The association of TRG with postoperative factors is listed in Table 3. TRG of the primary tumor was significantly related to the risk of residual tumor cells in resected lymph nodes: positive lymph nodes were found in 40.7% for TRG 0 + 1, 31.9% for TRG 2 + 3, and 10% for TRG 4 ($P = .001$), respectively. Complete resection of the primary tumor (R0) was achieved in 100% for TRG 4, 98% for TRG 2 + 3, and 92% for TRG 0 + 1 ($P = .012$). No significant associations were found for TRG and the interval between completion of CRT and surgery. Given that TRG 4 corresponds to ypT0, additional statistical analysis was restricted to TRG 0 + 1 and TRG 2 + 3 for this variable. Advanced ypT3 and ypT4 tumors after CRT were noted more frequently in the group of patients with TRG 0 + 1 compared with TRG 2 + 3 ($P = .03$). TRG 0 + 1 was also significantly associated with a higher risk of venous invasion ($P = .03$).

TRG As a Prognostic Factor for DFS

The 5-year DFS for 344 patients after curative surgery was 74%. Locoregional recurrence occurred in 10 patients: one patient had local recurrence alone, and nine also had distant recurrences. A total of 63 patients had only distant recurrences. By univariate analysis, TRG was found to be correlated significantly with DFS and metastases-free survival (Fig 2 and Table 4). None of the patients with TRG 4 experienced a local recurrence, whereas in 4% and 6% of patients with TRG 2 + 3 and TRG 0 + 1, respectively, a local recurrence occurred ($P = .33$). As listed in Table 4, other factors that correlated significantly with DFS by univariate analysis included the ypT and ypN category, International Union Against Cancer stage, tumor grade, and lymphatic and venous invasion. Only ypT, ypN, International Union Against Cancer stage, and lymphatic invasion were correlated significantly with the risk of a local recurrence. Using multivariate analysis, which included all significant factors on univariate analysis for the respective end points, we found that ypN positive was the strongest prognostic factor for all three end points (Table 5).

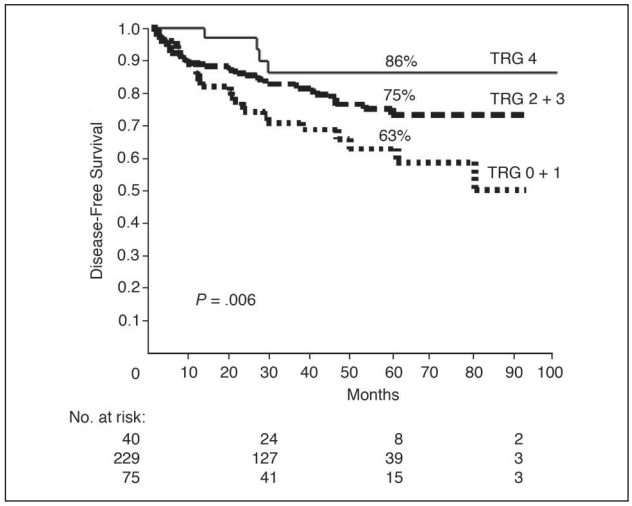

Fig 2. Disease-free survival of 344 patients with rectal carcinoma after preoperative chemoradiotherapy and curative resection (R0 resection), according to tumor regression grading (TRG).

Subgroup Analysis of Prognostic Factors for DFS

Given the strong prognostic impact of ypN positive for DFS, we investigated which factors may be prognostic in the more favorable subgroup of patients with negative lymph nodes. As seen in Table 6, node-negative tumors showing poor response (TRG 0 + 1) had a 5-year disease-free survival of 75% compared with 85% and higher for tumors with intermediate or complete tumor regression ($P = .11$). Histopathologic factors, such as ypT4, L1, and V1, also had lower 5-year DFS figures; however, no statistically significant correlation with DFS was noted. If ypT was included as a stratification factor for the TRG classification (Table 6, bottom), the 5-year DFS for patients with ypT3-4, pN0 tumors was 87% for TRG 2 + 3 and 71% for TRG 0 + 1 ($P = .13$). If analysis was restricted to identical TNM stages (eg, ypT3, pN0 tumors), the 5-year DFS was 88% for patients with TRG 2 + 3, and 69% for patients with TRG 0 + 1 ($P = .06$; data not shown in Table 6).

DISCUSSION

Histologic changes after preoperative CRT for rectal carcinoma vary considerably, with some entities showing complete absence of tumor cells, whereas others exhibit a mass of tumor cells with little or no regressive changes. Tumor regression is associated with treatment-related factors, such as overall doses of radiation, combination with chemotherapy, and the time interval between preoperative treatment and surgery.[14-16] Given that these factors were largely homogenous for all patients within our trial, it is likely that factors related to the individual tumor may have caused the observed differences in TRG.

Table 4. Impact of Different Clinical and Pathologic Factors on 5-Year Outcome After Preoperative Chemoradiotherapy and Curative R0-Resection (n = 344)

Factor	No. of Patients*	5-Year Disease-Free Survival (%)	*P*	5-Year Distant Metastases-Free Survival (%)	*P*	5-Year Local Relapse-Free Survival (%)	*P*
All	344	74		74		96	
Age, years							
≤ 61	182	74	.52	75	.44	94	.10
> 61	162	73		73		98	
Sex							
Male	246	73	.52	74	.46	97	.36
Female	98	74		74		94	
ypT category							
T0	40	86	< .0001	86	< .0001	100	.015
T1	20	95		95		100	
T2	110	81		83		97	
T3	166	65		65		94	
T4	8	42		38		86	
ypN category							
N0	247	85	< .0001	85	< .0001	99	< .0001
N1	57	65		65		93	
N2	40	18		24		78	
UICC TNM stage							
No tumor	36	85	< .0001	85	< .0001	100	.0008
I	102	89		89		100	
II	109	82		82		98	
III	97	46		48		88	
Grading							
1/2	239	73	.02	74	.02	95	.81
3/4	51	60		59		96	
Lymphatic invasion							
L0	271	80	< .0001	80	< .0001	98	.002
L1	67	51		53		86	
Venous invasion							
V0	331	74	.03	75	.03	96	.52
V1	13	49		49		100	
TRG							
4	40	86	.04	86	.07	100	.25
3	186	73		73		97	
2	43	83		83		92	
1	47	55		55		95	
0	28	78		85		93	
Grouped TRG							
4	40	86	.006	86	.009	100	.33
2 + 3	229	75		75		96	
0 + 1	75	63		66		94	

Abbreviations: UICC, International Union Against Cancer; TRG, tumor regression grading.
*Not all numbers in the respective variables add up to 344 patients because data with unknown factors (see Table 3) were excluded from analysis.

We found that complete regression of the primary tumor (TRG 4) was associated with better control of disease in lymph nodes (ypN positive, 10%), and finally resulted in sustained local control (100%) and a minor risk to develop distant metastases (DFS, 86%). Patients with tumors showing intermediate tumor regression (TRG 2 + 3) also had an intermediate risk of lymph node involvement (ypN positive, 32%), and yielded an intermediate prognosis (DFS, 75%). Poor tumor regression (TRG 0 + 1) was associated with adverse pathologic features, such as more advanced ypT categories, higher incidence of nodal involvement (ypN positive, 42%), and predicted for an unfavorable outcome (DFS, 63%). These findings are in accordance with observations in other malignancies, such as esophageal, gastric, bladder, and head and neck cancer, treated by preoperative radiotherapy or chemotherapy.[17-21] Overall, in these series, a higher grade of tumor regression predicted better survival.

What is the biologic background of this common phenomenon in oncology? Is tumor regression after preoperative treatment simply associated with smaller tumors or earlier

Table 5. Multivariate Analysis for Disease-Free, Metastases-Free, and Local Relapse-Free Survival After Preoperative Chemoradiotherapy and Curative R0 Resection (n = 344)

Variable	*P*	Reference Value for Hazard Ratio	Hazard Ratio	95% CI for Hazard Ratio
Disease-free survival				
ypT	.016	T increment	1.48	1.08 to 2.03
ypN	< .0001	N increment	2.68	2.03 to 3.54
Metastases-free survival				
ypT	.014	T increment	1.49	1.08 to 2.05
ypN	< .0001	N increment	2.59	1.95 to 3.43
Local relapse-free survival				
ypN	< .0001	N increment	3.86	1.83 to 8.16

stage? Janjan et al[4] and Willet et al[22] identified pretreatment tumor size as a significant factor for pathologic complete response after preoperative CRT in rectal cancer. In our study, the pretreatment tumor size (ie, the volume of the macroscopic tumor mass on CT/magnetic resonance imaging scans) was not documented. We found TRG not to be significantly related to specific pretreatment characteristics, such as the cT and cN categories. However, TRG 4 occurred more frequently in tumors with early T categories, which are—albeit not 100%—related to a smaller tumor size. Thus, the radiobiologic paradigm that eradication of a tumor by a given amount of radiation, among other factors, is dependent on its size may at least in part explain the observed association between T category, tumor regression, and prognosis.

The second hypothesis is that the extent of tumor regression is closely related to its aggressiveness and responsiveness toward CRT. It is noteworthy that tumor regression—an assessment of local treatment efficacy—was significantly associated with the risk of systemic tumor dissemination. Theoretically, local recurrences could be a source of secondary distant metastases; however, the number of local failures was too small in our cohort of patients to account for the observed differences in metastases-free survival. It is conceivable that local tumor regression may also predict responsiveness of disseminated tumor cells toward the fluorouracil component of our combined approach. However, in a series of 102 rectal cancer patients treated with preoperative radiotherapy alone, Bouzourene et al[23] also found a significant correlation between local tumor regression and DFS. Another important observation comes from studies on molecular markers that have been shown to predict radiosensitivity in rectal cancer. We and others have demonstrated previously that pretreatment apoptosis and apoptosis-related proteins strongly predicted TRG and DFS after preoperative CRT in rectal cancer.[24-26] More recent investigations showed that these molecular features also predicted clinical outcome in patients treated with surgery alone in the absence of any radiotherapy or chemotherapy.[27,28] It is our hypothesis from all these findings that tumor regression after preoperative CRT is a multifaceted phenomenon. It appears to be associated with smaller, less aggressive disease, and may also correspond to the molecular tumor profile regulating treatment response. Although these molecular profiles may also confer some survival advantage after surgery alone, this advantage is probably greatly augmented by treatment with cytotoxic agents.

It is clear from our results that there are multiple clinical and histopathologic factors that are relevant in determining prognosis after preoperative CRT. TRG alone is not definitive. Well-established histopathologic factors, in particular the ypT and ypN category, remain the most important prognostic factors.[29] Positive lymph nodes after preoperative CRT indicate both an aggressive potential of the malignant cells to spread to the regional lymph nodes and a resistance of these cells toward CRT. As a result, these patients have an unfavorable prognosis irrespective of any TRG of the primary tumor. For the more favorable subgroup of patients with negative lymph nodes, no clear statistically significant prognostic factor for DFS could be determined (Table 6). Of note, patients with lymph node–negative disease but poor tumor regression of the primary tumor showed a (not statistically significant) trend toward lower DFS rates compared with patients with intermediate/complete regression.

Some investigators have recommended local excision without lymphadenectomy when preoperative CRT has reduced the cancer to a scar.[30-32] Several series have established a direct correlation between the pathologic response of the primary tumor and the control of microscopic disease in perirectal lymph nodes.[33-36] However, in our study, the percentage of patients with involved lymph nodes reached 10% for ypT0 tumors, and even 25% (five of 20 patients; Table 6) for ypT1 tumors. Thus, caution should be exercised when considering less radical surgery after preoperative CRT. We currently are continuing to recommend definitive surgical resection for these patients as standard treatment regardless of treatment response.

If evaluation of TRG is to be implemented in pathologic reports, it is clear that a standardized method of assessing tumor response is required. Before issuing a ypT0 report, it is

Table 6. Impact of Different Clinical and Pathologic Factors on 5-Year Disease-Free Survival After Preoperative Chemoradiotherapy and Curative Resection, Adjusted to UICC TNM Stage 0-II and III, Respectively

Factor	UICC Stage 0-II			UICC Stage III		
	No. of Patients*	5-Year Disease-Free Survival (%)	*P*	No. of Patients*	5-Year Disease-Free Survival (%)	*P*
All	247	85		97	46	
ypT category						
T0	36	85	.20	4	100	.0022
T1	15	93		5	100	
T2	89	88		21	53	
T3	104	82		62	37	
T4	3	67		5	Not reached	
ypN category						
N0	247	85	NA		NA	< .0001
N1	NA	NA		57	65	
N2	NA	NA		40	18	
UICC TNM stage						
No tumor	36	85	.16		NA	NA
I	102	89			NA	
II	109	82			NA	
III	NA	NA		97	46	
Grading						
1/2	174	84	.56	65	45	.38
3/4	24	87		27	35	
Lymphatic invasion						
L0	214	86	.14	57	57	.04
L1	29	78		38	20	
Venous invasion						
V0	241	86	.22	90	47	.34
V1	6	67		7	24	
TRG						
4	36	85		4	100	
2 + 3	162	89	.11	67	43	.13
0 + 1	49	75		26	41	
Only ypT0-2						
4	36	85		4	100	
2 + 3	84	91	.98	21	61	.29
0 + 1	20	83		5	50	
Only ypT3-4						
4	NA	NA			NA	
2 + 3	78	87		46	35	.73
0 + 1	29	71	.13	21	39	

Abbreviations: UICC, International Union Against Cancer; NA, not applicable; TRG, tumor regression grading.
*Not all numbers in the respective variables add up to 344 patients because data with unknown factors (see Table 3) were excluded from analysis.

pivotal that the entire scarred area of the rectum needs to be blocked, sectioned at several levels, and scrutinized meticulously for any foci of tumor cells. In patients who achieve less than a pathologic complete regression, there is heterogeneity in scoring the presence of residual tumor. A five-point grading scale was first developed by Mandard et al[17] to assess response of preoperative CRT in esophageal cancer; however, only two groups of tumor regression grade were prognostically relevant (grades 1, 2, 3 *v* 4, 5). It needs to be emphasized that the TRG grouping chosen for our analysis, TRG 4 *v* 2 + 3 *v* 0 + 1, has led to stronger results than would have been obtained through other groupings. Thus, these results need to be considered exploratory and the hypotheses generated by our TRG grouping need to be validated in additional data sets. A similar 3-point Rectal Cancer Regression Grade was also suggested recently by Wheeler and al.[9] Clearly, the accuracy, reliability, and validity of these new techniques need to be investigated further.

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Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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