A Modified Classification of Prognostic Factors Based on Pathological Stage and Tumor Regression Grade in Patients with Rectal Cancer Who Receive Preoperative Chemoradiotherapy

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Keywords

Rectal cancer · Chemoradiotherapy · Prognostic factor · Tumor regression grade · ypStage

Abstract

Objective: The histologic response to neoadjuvant chemoradiotherapy (CRT) has been intimately related to outcomes in locally advanced rectal cancer. However, reliable prognostic factors have yet to be established. **Subjects and Methods:** The study group comprised 198 patients with locally advanced rectal cancer who received CRT. A modified classification based on the combination of ypStage and tumor regression grade (TRG) was developed. ypStage II with TRG 2 was classified as ypTRGstage IIA, and ypStage II with TRG 3 or 4 was classified as ypTRGstage IIB. ypStage 0 and ypStage I were classified as ypTRGstage I, and ypStage III was classified as ypTRGstage III. **Results:** The 5-year disease-free survival (DFS) was 83% in ypTRGstage I, 86% in ypTRGstage IIA, 57% in ypTRGstage IIB, and 60% in ypTRGstage III ($p = 0.0001$). The 5-year DFS in ypTRGstage IIA did not differ significantly from that in ypStage 0 ($p = 0.865$) or ypStage I ($p = 0.585$). The 5-year DFS in ypStage IIB did not differ from that in ypStage III ($p = 0.912$). Multivariate analysis showed that ypTRGstage was an independent risk factor for DFS. **Conclusion:** A mod-

ified classification allows patients with ypStage II locally advanced rectal cancer to be clearly divided into two groups: responders and nonresponders.

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Introduction

Multidisciplinary treatment including preoperative radiotherapy is the global standard for T3, N0 or T_{any}, N1–2, or T4 rectal cancer and significantly decreases local recurrence [1–4]. However, the European Society for Medical Oncology (ESMO) guidelines [5] claim that clinical T3a or T3b, N0 cancer of the middle or higher rectum has a good outcome and can therefore be treated by surgery alone.

The histologic response to preoperative chemoradiotherapy (CRT) in the radiation field has been reported to be closely related to outcomes. Patients who have post-treatment pathological complete regression, a marked decrease in tumor volume, or downstaging of T or N stage have been shown to have significantly better disease-free survival (DFS) and overall survival (OS) than patients without these findings [6–10].

However, ypStage II disease includes patients who initially have pT3–T4, N1 disease and show a good response to treatment, resulting in downstaging, patients who initially have pT3–T4, N0 disease who respond to treatment without downstaging, and patients who initially have pT3–T4, N0 disease and show a poor response to treatment. We therefore hypothesized that a new classification more closely related to outcomes could be developed by dividing patients with ypStage II disease into two groups: those with a good histologic response and those with a poor histologic response. We thus designed a modified classification based on the posttreatment pathological stage (ypStage) and tumor regression grade (TRG).

Subjects and Methods

Between 2007 and 2015, total mesorectal excision surgery combined with preoperative CRT was used to treat 198 patients with histologically proven adenocarcinoma of the middle or lower rectum who had a preoperative diagnosis of clinical stage (cStage) II or stage III disease according to the TNM classification.

The initial evaluation included digital examination of the rectum, colonoscopy, barium enema, computed tomography of the chest, abdomen, and pelvis, endorectal ultrasonography, and magnetic resonance imaging of the pelvis.

Chemoradiotherapy

Preoperative radiotherapy was performed with 18-MV X-ray beams delivered by a linear accelerator (Clinac 2100C; Varian Medical Systems, Inc., Palo Alto, CA, USA) using a four-field technique. Irradiation was performed once (1.8 or 2 Gy) daily to a total dose of 40–45 Gy. Total mesorectal excision surgery was done 6–8 weeks (range, 30–65 days) after the completion of irradiation.

Concomitant chemotherapy with oral uracil-tegafur (400 mg/m²) or oral S-1 (80 mg/m²) was started at the same time as radiotherapy. Oral uracil-tegafur was simultaneously given with radiotherapy on 5 weekdays, followed by a 2-day rest on weekends. This cycle was repeated during irradiation. Oral S-1 (80 mg/m²) was simultaneously started with radiotherapy. S-1 was given for 2 consecutive weeks, followed by a 1-week rest, and was then given for another 2 weeks [11, 12].

Histologic regression was assessed using the Mandard TRG [13] as follows: TRG 1, complete regression; TRG 2, presence of rare residual cancer cells; TRG 3, fibrosis outgrowing residual cancer cells; TRG 4, residual cancer cells outgrowing fibrosis; and TRG 5, absence of regression.

We designed a modified classification based on the TRG that classified patients with ypStage II disease into two groups. Patients with TRG 2 were classified as ypTRGstage IIA, and those with TRG 3 or 4 were classified as ypTRGstage IIB (Table 1).

Statistical Analysis

Statistical analysis was performed using SPSS for Windows, version 23 (IBM Japan, Ltd., Tokyo, Japan). Actuarial survival curves were calculated according to the Kaplan-Meier method. The probabilities of DFS and OS were determined by log-rank

Table 1. Modified prognostic classification consisting of ypStage and TRG

ypTRGstage I	ypStage 0, I
ypTRGstage IIA	ypStage II + TRG 2
ypTRGstage IIB	ypStage II + TRG 3, 4
ypTRGstage III	ypStage III
TRG, tumor regression grade.	

analysis. A Cox proportional hazards model was used to adjust comparisons for clinicopathological variables. *p* values <0.05 were considered to indicate statistical significance.

Results

Patient and Tumor Characteristics

Table 2 shows the patient characteristics. There were 150 men and 48 women with a median age of 64 years. Overall, 85 patients had clinical stage II disease and 113 had clinical stage III disease. The chemotherapeutic drugs administered concurrently with preoperative radiotherapy were S-1 in 153 patients (77.3%) and uracil-tegafur in 45 patients (22.7%). Sphincter-preserving surgery was performed in 147 patients (74.2%). Before CRT, 96.5% of the patients had clinical T3 or T4 disease, and 57.1% had clinical N1 or cN2 disease. After CRT, however, the proportion of patients with pathological T3 or T4 disease decreased to 51.5%, and the proportion of patients with pathological N1 or N2 disease decreased to 22.7%.

Pathological complete response (pCR) was found in 31 patients (15.7%). One patient had complete regression (TRG 1) of the primary lesion, but was pathologically node-positive (pN+). Among the 40 patients with pathological T0 disease, 8 had carcinoma in situ (Tis).

The TRG was TRG 1 in 32 patients (16.2%), TRG 2 in 52 patients (26.3%), TRG 3 in 78 patients (39.4%), and TRG 4 in 36 patients (18.2%). No patient had TRG 5. The ypStage was ypStage 0 in 39 patients (19.7%), ypStage I in 49 patients (24.7%), ypStage II in 65 patients (32.8%), and ypStage III in 45 patients (22.7%). Overall, 88 patients had ypTRGstage I, consisting of ypStage 0 and I combined. The 65 patients with ypStage II were classified into 16 patients with ypTRGstage IIA and 49 patients with ypTRGstage IIB. Forty-five patients had ypTRGstage III, which was identical to ypStage III.

Table 2. Patient characteristics

	<i>n</i> (%) or median (range)		<i>n</i> (%) or median (range)
Gender		ypT	
Male	150 (75.8%)	0	40 (20.2%)
Female	48 (24.2%)	1	13 (6.6%)
Age, years	64 (32–92)	2	43 (21.7%)
Tumor location		3	98 (49.5%)
Middle rectum	78 (39.4%)	4	4 (2.0%)
Lower rectum	120 (60.6%)	ypN	
Histologic type		0	153 (77.3%)
Well	144 (72.7%)	1	31 (15.7%)
Moderate	52 (26.3%)	2	14 (7.0%)
Poor	2 (1.0%)	Lymphatic invasion	
Clinical T stage		(–)	135 (68.2%)
2	7 (3.5%)	(+)	63 (31.8%)
3	159 (80.3%)	Venous invasion	
4	32 (16.2%)	(–)	120 (60.6%)
Clinical N stage		(+)	78 (39.4%)
0	85 (42.9%)	TRG	
1	73 (36.9%)	1	32 (16.2%)
2	40 (20.2%)	2	52 (26.3%)
Clinical stage		3	78 (39.4%)
II	85 (42.9%)	4	36 (18.2%)
III	113 (57.1%)	5	0 (0%)
Radiation dose		ypStage	
40 Gy	14 (7.1%)	0	39 (19.7%)
45 Gy	184 (92.9%)	I	49 (24.7%)
Concurrent chemotherapy		II	65 (32.8%)
Uracil-tegafur	45 (22.7%)	III	45 (22.7%)
S-1	153 (77.3%)	ypTRGstage	
Surgical procedure		I	88 (44.4%)
Low anterior resection	147 (74.2%)	IIA	16 (8.1%)
Abdominoperineal resection	51 (25.8%)	IIB	49 (24.7%)
Adjuvant chemotherapy		III	45 (22.7%)
Administered	117 (59.1%)		
Not administered	81 (40.9%)		

Lower rectum, lower third of the rectum; middle rectum, middle third of the rectum; TRG, tumor regression grade.

Survival Analysis

The median follow-up was 52 months (range, 1–168). The 5-year DFS was 71%, and the 5-year OS was 85%. Recurrence was found in 48 patients (24.2%). The initial site of recurrence was locoregional in 6 patients (3.0%), the liver in 17 patients (8.6%), the lung in 19 patients (9.6%), and distant lymph nodes in 6 patients (3.0%).

The 5-year DFS rate according to the TRG was as follows: TRG 1, 89%; TRG 2, 76%; TRG 3, 67%; and TRG 4, 59%. The 5-year OS rate according to the TRG was as follows: TRG 1, 96%; TRG 2, 82%; TRG 3, 84%; and TRG 4, 83%. Marked tumor regression (TRG 1 or 2) was con-

trasted with TRG 3 or 4. The DFS rate was significantly higher in patients with TRG 1 or 2 than in those with TRG 3 or 4 ($p = 0.014$). The OS rate did not differ between these groups ($p = 0.744$).

The 5-year DFS rate according to the ypStage was as follows: ypStage 0, 88%; ypStage I, 78%; ypStage II, 64%; and ypStage III, 60% ($p = 0.002$) (Fig. 1a). The 5-year OS rate according to ypStage was as follows: ypStage 0, 97%; ypStage I, 86%; ypStage II, 83%; and ypStage III, 80% ($p = 0.220$) (Fig. 1b).

The 5-year DFS rate according to the ypTRGstage was as follows: ypTRGstage I, 83%; ypTRGstage IIA,

Fig. 1. Disease-free survival (**a**) and overall survival (**b**) according to ypStage. 5y DFS, 5-year disease-free survival; 5y OS, 5-year overall survival.

Fig. 2. Disease-free survival (**a**) and overall survival (**b**) according to ypTRGstage. 5y DFS, 5-year disease-free survival; 5y OS, 5-year overall survival.

86%; ypTRGstage IIB, 57%; and ypTRGstage III, 60% ($p = 0.0001$) (Fig. 2a). The 5-year OS rate according to the ypTRGstage was as follows: ypTRGstage I, 90%; ypTRGstage IIA, 100%; ypTRGstage IIB, 77%; and ypTRGstage III, 80% ($p = 0.029$) (Fig. 2b).

When ypStage was compared with ypTRGstage, the 5-year DFS rate in ypTRGstage IIA did not differ from

that in ypStage 0 ($p = 0.865$) or ypStage I ($p = 0.585$), and the 5-year DFS rate in ypTRGstage IIB did not differ from that in ypStage III ($p = 0.912$). Similarly, the 5-year OS rate in ypTRGstage IIA did not differ from that in ypStage 0 ($p = 0.520$) or ypStage I ($p = 0.179$), and the 5-year OS rate in ypTRGstage IIB did not differ from that in ypStage III ($p = 0.595$).

The 65 patients with ypStage II, comprising the largest subgroup of patients according to ypStage, could be classified into 16 patients with ypTRGstage IIA and a good prognosis and 49 patients with ypTRGstage IIB and a poor prognosis.

Prognostic Factors Affecting Survival

TRG 1 and 2, ypStage 0 and I, and ypTRGstage 0, I, and IIA were collectively considered to indicate a good response. Cox univariate analysis was performed to assess the relations of these variables to DFS. DFS correlated with ypT, post-CRT pathological nodal status (ypN), lymphatic invasion, venous invasion, TRG, ypStage, and ypTRGstage (Table 3).

Significant factors in the Cox univariate analysis were included in multivariate analysis. The results showed that ypT, ypN, and ypStage correlated with each other. Since ypT, ypN, TRG, and ypTRGstage correlated with each other, three types of multivariate analyses were performed (Table 4). The results showed that ypT, ypStage, and ypTRGstage were independent risk factors for DFS. The hazard ratio of ypTRGstage was 2.876 (95% confidence interval, 1.510–5.477), which was greater than the hazard ratio of ypStage (2.274; 95% confidence interval, 1.152–4.488).

Cox univariate analysis showed that OS was related to ypT, lymphatic invasion, ypStage, and ypTRGstage. Multivariate analysis showed that lymphatic invasion was an independent risk factor for OS (Table 5).

Discussion

Previous studies have reported that post-CRT ypT, ypN, ypStage, and histologic response (TRG) are related to oncologic outcomes [6, 8, 10, 14–21]. A four-level subclassification of the depth of extramucosal invasion has been proposed for pathological T stage (pT stage) [22]. In patients who are treated by surgery alone, DFS differs according to the subclassification of pT, but does not differ in patients who have received preoperative CRT. Therefore, pT has been reported not to be a prognostic factor [23, 24].

The TRG has been widely used to evaluate the histologic response to preoperative CRT. Quah et al. [25] reported that ypStage was more strongly associated with DFS than was TRG in 342 patients with rectal cancer who received preoperative CRT.

Patients with pCR [6, 8, 16, 18, 26–28] and those with good tumor regression even in the absence of pCR [8, 16,

Table 3. Univariate Cox proportional hazards regression model of clinical factors of disease-free survival

	<i>n</i> (%) or median (range)	<i>p</i> value	HR	95% CI
Gender				
Male	150 (75.8%)		1	
Female	48 (24.2%)	0.654	1.164	0.599–2.263
Age, years	64 (32–92)	0.865	0.951	0.533–1.695
Tumor location				
Middle rectum	78 (39.4%)		1	
Lower rectum	120 (60.6%)	0.196	1.459	0.823–2.588
Histologic type				
Well	144 (72.7%)		1	
Moderate/poor	54 (27.3%)	0.155	1.497	0.858–2.610
Clinical T stage				
2	7 (3.5%)		1	
3	159 (80.3%)	0.667	0.732	0.177–3.031
4	32 (16.2%)	0.818	0.836	0.182–3.834
Clinical N stage				
(–)	85 (42.9%)		1	
(+)	113 (57.1%)	0.958	1.014	0.592–1.738
Clinical stage				
II	85 (42.9%)		1	
III	113 (57.1%)	0.958	1.014	0.592–1.738
Radiation dose				
40 Gy	14 (7.1%)		1	
45 Gy	184 (92.9%)	0.105	0.527	0.244–1.142
Concurrent chemotherapy				
Uracil-tegafur	45 (22.7%)		1	
S-1	153 (77.3%)	0.673	0.870	0.457–1.658
ypT				
0, 1, 2	96 (48.5%)		1	
3, 4	102 (51.5%)	<0.001	3.329	1.820–6.089
ypN				
(–)	153 (77.3%)		1	
(+)	45 (22.7%)	0.012	2.048	1.173–3.578
Lymphatic invasion				
(–)	135 (68.2%)		1	
(+)	63 (31.8%)	0.001	2.511	1.478–4.266
Venous invasion				
(–)	120 (60.6%)		1	
(+)	78 (39.4%)	0.014	1.946	1.144–3.310
TRG				
1, 2	84 (42.4%)		1	
3, 4, 5	114 (57.6%)	0.016	2.081	1.148–3.772
ypStage				
0/I	88 (44.4%)		1	
II/III	110 (55.6%)	<0.001	3.069	1.651–5.704
ypTRGstage				
I/IIA	104 (52.5%)		1	
IIB/III	94 (47.5%)	<0.001	3.590	1.989–6.481

CI, confidence interval; HR, hazard ratio; lower rectum, lower third of the rectum; middle rectum, middle third of the rectum; TRG, tumor regression grade.

17, 21, 26, 28–31] have been reported to have good outcomes. Agarwal et al. [28] studied 251 patients with locally advanced rectal adenocarcinoma who received preoperative CRT and found that recurrence-free survival

Table 4. Multivariate Cox proportional hazards regression model of clinical factors of disease-free survival

	<i>n</i> (%)	<i>p</i> value	HR	95% CI
ypT				
0, 1, 2	96 (48.5%)		1	
3, 4	102 (51.5%)	0.008	2.511	1.278–4.933
ypN				
(–)	153 (77.3%)		1	
(+)	45 (22.7%)	0.797	1.089	0.568–2.086
Lymphatic invasion				
(–)	135 (68.2%)		1	
(+)	63 (31.8%)	0.134	1.648	0.858–3.168
Venous invasion				
(–)	120 (60.6%)		1	
(+)	78 (39.4%)	0.873	1.052	0.561–1.974
TRG				
1, 2	84 (42.4%)		1	
3, 4, 5	114 (57.6%)	0.612	1.190	0.607–2.334
Lymphatic invasion				
(–)	135 (68.2%)		1	
(+)	63 (31.8%)	0.084	1.707	0.931–3.131
Venous invasion				
(–)	120 (60.6%)		1	
(+)	78 (39.4%)	0.753	1.104	0.596–2.045
TRG				
1, 2	84 (42.4%)		1	
3, 4, 5	114 (57.6%)	0.593	1.201	0.613–2.353
ypStage				
0/I	88 (44.4%)		1	
II/III	110 (55.6%)	0.018	2.274	1.152–4.488
Lymphatic invasion				
(–)	135 (68.2%)		1	
(+)	63 (31.8%)	0.116	1.614	0.888–2.933
Venous invasion				
(–)	120 (60.6%)		1	
(+)	78 (39.4%)	0.736	1.107	0.614–1.995
ypTRGstage				
I/IIA	104 (52.5%)		1	
IIB/III	94 (47.5%)	0.001	2.876	1.510–5.477

CI, confidence interval; HR, hazard ratio; TRG, tumor regression grade.

did not differ between patients with pCR and those with nearly complete response (residual cancer cells $\leq 5\%$). Guillem et al. [8] studied 297 patients with rectal cancer who received preoperative CRT and reported that the survival rate was significantly higher in patients with pCR or nearly pCR ($\geq 95\%$ tumor response) than in patients with other responses.

On the basis of these results, evaluation methods combining ypStage and TRG have been studied to identify better prognostic factors. Cui et al. [30] studied 329 patients with clinical stage II or III rectal adenocarcinoma who received preoperative CRT and developed a modified T stage classification metric (M-TTRG) that catego-

Table 5. Disease-free survival according to TRG, ypStage and ypTRGstage

	1-year DFS	3-year DFS	5-year DFS
TRG			
1, 2	94%	85%	81%
3, 4, 5	86%	69%	64%
ypStage			
0/I	99%	86%	83%
II/III	82%	67%	62%
ypTRGstage			
I/IIA	98%	86%	83%
IIB/III	80%	64%	59%

DFS, disease-free survival; TRG, tumor regression grade.

rized patients into five subgroups on the basis of ypT stage and TRG. This system was combined with ypN stage to develop a modified ypTNM staging system that categorizes patients into seven subgroups. However, this system is very complex.

Some patients with ypStage II histologically have a nearly pCR without downstaging owing to the presence of small amounts of cancer cells in extramuscular tissue. The ypTRGstage that we proposed allowed patients with ypStage II to be classified into two subgroups: patients with ypStage II who have a good response to treatment with no downstaging and patients with ypStage II who have a poor response to treatment. This classification of responders and nonresponders was more closely related to outcomes.

In patients who have received neoadjuvant chemotherapy, the indications for and regimens of postoperative adjuvant chemotherapy remain controversial [32, 33]. In the present study, the rate of adjuvant chemotherapy was 44% in ypStage 0 or I disease, 60% in ypStage II or III disease, 45% in ypTRGstage I or IIA disease, and 62% in ypTRGstage IIB or III disease. The rates of adjuvant chemotherapy were significantly higher in ypStage II or III disease ($p = 0.040$) and in ypTRGstage IIB or III disease ($p = 0.029$).

Our study was retrospective and has several important limitations. It was performed in a single hospital and included only 198 patients. Further multicenter studies of larger number of patients are needed to verify our results.

The ypTRGstage consists of four classes. The survival rate did not differ between ypTRGstage I and IIA, associated with a good response, or between ypTRGstage IIB and III, associated with a poor response. Further studies are therefore needed to determine whether patients who

have ypTRGstage I and IIA can be simply classified as responders and those with ypTRGstage IIB and III as non-responders.

Conclusions

A modified classification based on the combination of ypStage and TRG as prognostic factors allowed patients with ypStage II locally advanced rectal cancer who received neoadjuvant CRT to be classified into good and poor responders. This classification is a useful straightforward method for predicting outcomes.

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Statement of Ethics

This study was approved by the institutional review board of Tokai University (08R-032), and all patients provided written informed consent.

Disclosure Statement

The authors report no potential conflicts of interest.

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