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Oncological Outcomes of Pathological T1 Lower Rectal Cancer Patients With or Without Preoperative Chemoradiotherapy

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Abstract. *Background/Aim: It remains unclear whether rectal cancers down-staged by preoperative chemoradiotherapy (CRT) have similar prognoses to those of the same stage without preoperative CRT. We compared prognoses of pT1 rectal cancer patients stratified by preoperative CRT. Patients and Methods: We retrieved data of patients with pathological T1 rectal cancer between 2003 and 2020. Patients were divided into the "ypT1 group" who received preoperative CRT following surgery and the "pT1 group" who underwent surgery alone. Factors associated with relapse-free survival (RFS) were investigated. Results: Among 86 patients, ypT1 and pT1 groups comprised 18 and 68 patients, respectively. There was no significant difference in RFS between the groups (p=0.19). Tumor location within 5 cm from the anal verge was associated with recurrence (hazard ratio: 0.13, p=0.034). Conclusion: The prognosis of patients with ypT1 rectal cancer was similar to that of patients with pT1. Low tumor location was a poor prognostic factor.*

Colorectal cancer is the third most commonly diagnosed cancer in males and the second in females worldwide (1). The management of rectal cancer requires multidisciplinary approaches (2). In rectal cancer that does not invade beyond the proper muscle layer, a good prognosis can be achieved by local excision or total mesorectal excision (TME) alone without preoperative chemoradiotherapy (CRT) (3, 4). In contrast, preoperative CRT followed by TME is one of the standard treatments for rectal cancer that penetrates the proper muscle layer (5). Preoperative CRT can reduce the local recurrence rate and increase the rate of sphincter preservation with a lower toxicity rate than postoperative CRT (6-9). A pathological complete response can be achieved in 10-20% of patients receiving preoperative CRT and is associated with excellent oncological outcomes (10-13). In addition, approximately 40-60% patients demonstrated down-staging after preoperative CRT (14-16). These rectal cancer patients who exhibited a good response to preoperative CRT also had a favorable prognosis (17-19).

Several studies have reported that the pathological stage was a better predictor for disease-free and overall survival than preoperative stage or response to CRT in rectal cancer patients who received preoperative CRT (14, 20-22). However, it remains unclear whether rectal cancer down-staged by preoperative CRT has a different prognosis from that of the same stage without preoperative CRT. Several groups have previously conducted comparative studies of patients with pathological stage I lower rectal cancer according to preoperative CRT, but the conclusions regarding their prognoses were inconsistent (23-27). Moreover, no similar study confined to pT1 stage has been conducted.

In the current study, we investigated the prognoses of pT1 rectal cancer patients with or without preoperative CRT, and identified prognostic factors among clinicopathological variables.

Patients and Methods

Patients and clinicopathological parameters. In this retrospective study, we reviewed consecutive patients who had pathological T1 rectal adenocarcinoma located in the lower rectum that was resected by radical surgery at the Department of Surgical Oncology, the University of Tokyo Hospital between August 2003 and January 2020. Patients who underwent trans-anal local excision were excluded from this study. Patients with rectal cancer associated with inflammatory bowel disease and those with suspected lateral pelvic lymph node and/or distant metastases were also excluded.

All resected specimens were assessed pathologically in accordance with the eighth edition of the American Joint Committee on Cancer (28).

The following variables were collected from the medical records: date of operation, sex, age, body mass index (BMI), Eastern

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Key Words: Preoperative chemoradiotherapy, rectal cancer, prognosis.

Cooperative Oncology Group (ECOG) Performance Status (PS), tumor location from the anal verge, tumor size, preoperative serum carcinoembryonic antigen (CEA, the upper limit of normal: 5 ng/ml), surgical procedure, clinical T and N stages, pathological N stage, number of lymph nodes dissected, histological type, lymphatic invasion, venous invasion, and adjuvant chemotherapy (AC). This study was approved by the ethics committee of the University of Tokyo [No. 3252-(10)].

Pretreatment evaluation, preoperative CRT, and surgery. Before treatment, patients were assessed using physical examination, colonoscopy, chest-to-pelvic computed tomography (CT), pelvic magnetic resonance imaging (MRI), and positron emission tomography (PET).

When diagnosed with adenocarcinoma of the rectum with clinical T3 or T4 stage and/or regional lymph node metastases, patients received preoperative CRT. CRT consisted of a total dose of 50.4 Gy of radiation using the 4-field box technique and concomitant 5-fluorouracil (5-FU) - based chemotherapy. Surgery was performed 6-10 weeks after the completion of CRT.

All patients underwent radical surgery based on TME. The surgical procedures included lower anterior resection (LAR), intersphincteric resection (ISR), abdominoperineal resection (APR), and the Hartmann's operation.

Patient classification. Patients who received preoperative CRT and TME-based surgery were classified into the "ypT1 group", whereas those treated by surgery alone were classified into the "pT1 group".

Postoperative follow-up. Whether AC was prescribed to patients was at the doctor's discretion and depended on the patients' preference. All patients underwent a standardized follow-up schedule that included physical examination and serum CEA levels assessment every three months, CT every six months, and annual colonoscopy for at least five years after surgery. Oncological outcomes were evaluated by assessing relapse-free survival (RFS), which was defined as the time between the initial surgery and the date of diagnosis of tumor recurrence in any organ.

Statistical analysis. Categorical variables were compared using the chi-squared or Fisher's exact test. Continuous variables were compared using the unpaired t or Mann-Whitney *U*-test. Factors associated with RFS were estimated by univariate and multivariate analyses using the Cox proportional hazards model, where continuous variables were dichotomized by their median or mean values, except for CEA (5 ng/ml) and the number of lymph nodes dissected (12). Only the variables with $p<0.10$ by the univariate analysis were subjected to the multivariate analysis. RFS curves were estimated using the Kaplan-Meier method and compared using the log-rank test. All analyses were performed using the JMP Pro 15.1 software (SAS Institute Inc, Cary, NC, USA); *p*-values <0.05 were considered significant.

Results

Patient characteristics. As shown in Figure 1, we identified 86 eligible patients. There were 18 patients in the ypT1 group and 68 patients in the pT1 group. The clinical and pathological characteristics were compared between the ypT1 and pT1 groups (Table I). The clinical T stage ($p<0.001$) and N stage ($p<0.001$) were more advanced in the ypT1 group than in the pT1 group. However, venous invasion was more frequent in the pT1 group than in the ypT1 group (59% *vs*. 28%; $p=0.032$). No significant difference was observed in the other preoperative and pathological factors between the two groups.

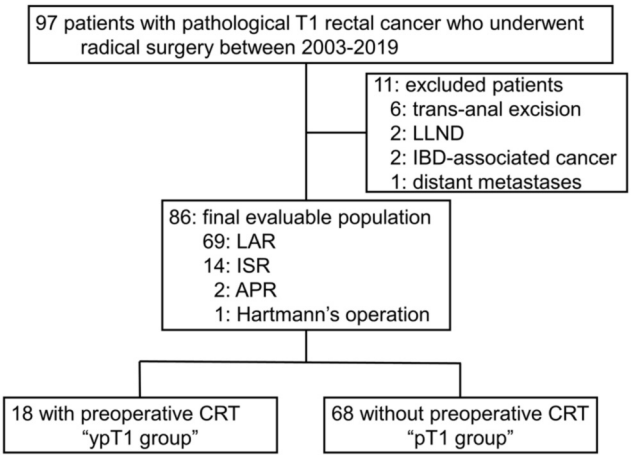

Figure 1. *Flowchart of patient enrollment and definition of patient subgroups. LLND: Lateral lymph node resection; IBD: inflammatory bowel disease; LAR: low anterior resection; ISR: intersphincteric resection; APR: abdominoperineal resection; CRT: chemoradiotherapy; yp: pathological data following preoperative chemoradiotherapy; p: pathological data.*

Follow-up and recurrence. Only one patient (6%) in the ypT1 group was administered oral 5-FU as AC for six months. No patient in the pT1 group received AC. During the follow-up period (median: 51.1 months for the entire population), three patients in the pT1 group developed recurrence; the involved organs were the lung in two patients and para-aortic lymph nodes in one. No patient in the ypT1 group developed recurrence.

Factors associated with relapse-free survival. To identify prognostic factors associated with RFS, univariate and multivariate analyses were performed. As shown in Table II, tumor location within 5 cm from the anal verge was a significant factor associated with a poor RFS on univariate analysis ($p=0.020$). In addition, the body mass index and preoperative CRT were weakly associated with RFS ($p=0.076$ and $p=0.084$, respectively). By multivariate analysis, only the distance from the anal verge was an independent predictor of RFS (hazard ratio: 0.13, $p=0.034$).

Relapse-free survival curves by comparison groups. RFS was compared according to preoperative CRT and tumor location. The RFS curve for the ypT1 group did not differ from that for the pT1 group (3-year RFS rate: 100% *vs*. 92%, $p=0.19$; Figure 2A). However, the RFS curve for patients with rectal

Table I. *Patient characteristics*.

Characteristics	ypT1 (n=18)	pT1 (n=68)	*p*-Value
Date of operation			0.062
2003-2014	12 (67%)	27 (40%)	
2015-2020	6 (33%)	41 (60%)	
Gender			0.12
Male	7 (39%)	41 (60%)	
Female	11 (61%)	27 (40%)	
Age, mean±SD (years)	66±2.6	61±1.3	0.13
BMI, mean±SD (kg/m^2)	22.6±0.8	23.4±0.4	0.34
ECOG PS			1.00
0	18 (100%)	66 (97%)	
1-2	0	2 (3%)	
Distance from anal verge, mean±SD (cm)	5.8±0.5	5.4±0.3	0.44
Size of tumor, mean±SD (mm)	17.9±3.1	20.3±1.6	0.50
Preoperative CEA (ng/ml)			0.23
<5	14 (78%)	61 (90%)	
≥5	4 (22%)	7 (10%)	
Surgical procedure			0.67
LAR	15 (83%)	54 (79%)	
ISR	2 (11%)	12 (18%)	
APR	1 (6%)	1 (1%)	
Hartmann	0	1 (1%)	
Clinical T stage			<0.001
cT0/cTis	0	10 (15%)	
cT1	0	43 (63%)	
cT2	1 (5%)	15 (22%)	
cT3	16 (90%)	0	
cT4	1 (5%)	0	
Clinical N stage			<0.001
cN–	13 (72%)	68 (100%)	
cN+	5 (28%)	0	
No. of LNs dissected			0.60
<12	10 (56%)	31 (46%)	
≥12	8 (44%)	37 (54%)	
Histological type			0.58
Differentiated	18 (100%)	64 (94%)	
Others	0	4 (6%)	
Lymphatic invasion			0.18
Absent	17 (94%)	54 (79%)	
Present	1 (6%)	14 (21%)	
Venous invasion			0.032
Absent	13 (72%)	28 (41%)	
Present	5 (28%)	40 (59%)	
Adjuvant chemotherapy			0.21
No	17 (94%)	68 (100%)	
Yes	1 (6%)	0	

P: Pathological data; yp: pathological data following preoperative chemoradiotherapy; SD: standard deviation; BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; CEA: carcinoembryonic antigen; c, clinical data; LAR: low anterior resection; ISR: intersphincteric resection; APR: abdominoperineal resection; LN: lymph node.

cancer located within 5 cm from the anal verge was markedly lower than that for the remaining patients (3-year RFS rate: 85% *vs*. 100%, p=0.014; Figure 2B).

Table II. *Univariate and multivariate analyses of prognostic factors of relapse-free survival*.

Characteristics	Univariate	Multivariate		
	p-Value	HR	95%CI	*p*-Value
Date of operation (2015-2020 *vs*. 2003-2014)	0.79			
Gender (male *vs*. female)	0.24			
Age (≥63 *vs*. <63 years)	0.63			
BMI (<23 *vs*. ≥23 kg/m^2)	0.076	0.19	0.01-1.28	0.090
ECOG PS (1-2 *vs*. 0)	0.81			
Distance from anal verge (≥5 *vs*. <5 cm)	0.020	0.13	0.01-0.86	0.034
Tumor size (≥20 *vs*. <20 mm)	0.64			
Preoperative CEA (≥5 *vs*. <5 ng/ml)	0.23			
Clinical T stage (cT2-4 *vs*. cT0-1)	0.34			
Clinical N stage (cN+ *vs*. cN–)	0.41			
No. of LNs dissected (≥12 *vs*. <12)	0.21			
Histological type (others *vs*. differentiated)	0.60			
Lymphatic invasion (present *vs*. absent)	0.74			
Venous invasion (present *vs*. absent)	0.70			
Preoperative CRT (present *vs*. absent)	0.084	<0.01	<0.01-1.47	0.095

HR: Hazard ratio; CI: confidence interval; BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; CEA: carcinoembryonic antigen; LN: lymph node; CRT: chemoradiotherapy.

Discussion

There are limited studies comparing the prognosis of stage I rectal cancer after preoperative CRT (ypT1-2N0M0) with that of treatment-naïve stage I rectal cancer (pT1-2N0M0) (23-27). Wan *et al*. have reported that ypStage I rectal cancer patients had shorter cancer-specific and overall survivals than pStage I patients by analyzing the Surveillance, Epidemiology, and End Results (SEER) registered database (25). However, in their study, the frequency of ypT2 was 61.2%, a markedly higher percentage than that of pT2 (33.1%, p<0.001). Li *et al*. have used propensity score-matching to analyze 168 matched pairs of rectal cancer patients with ypStage I and pStage I, and demonstrated similar prognoses; however, 45.2% of ypStage I patients were treated using AC whereas no pStage I patients received AC, which may have influenced the survival outcomes (27). Moreover, this propensity score matching study and three other reports included only a few (five or less) ypT1 patients (23, 24, 26, 27). To our best knowledge, the current study is the first to compare the prognosis of only

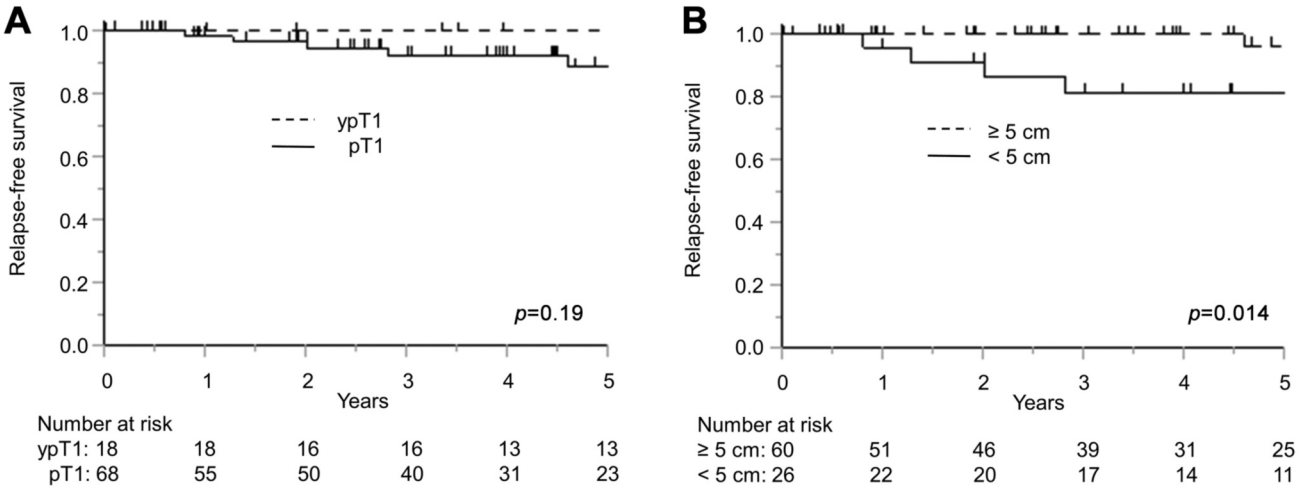

Figure 2. *Relapse-free survival (RFS) curves of rectal cancer patients with pathological T1 stage. A) RFS curves stratified by preoperative chemoradiotherapy (ypT1 vs. pT1). B) RFS curves stratified by tumor location from the anal verge (<5 cm vs. ≥5 cm).*

rectal cancer patients with pathological T1 stage, including 18 ypT1 patients. We did not observe a difference in RFS between ypT1 and pT1 patients. In addition, preoperative CRT was not a significant factor for RFS.

In the current study, rectal cancer located within 5 cm from the anal verge was independently associated with recurrence (hazard ratio: 0.13, p=0.034). Chiang *et al*. have reported that T3-4 cancers of the lower rectum had a significantly poorer disease-free survival than those of the upper rectum without neoadjuvant therapy (29). Cheng *et al*. have found that a tumor location within 10 cm from the anal verge was associated with poor overall survival in stage III rectal cancer without neoadjuvant therapy (30). However, the association between the location of rectal cancer and RFS has not been investigated among patients receiving neoadjuvant therapy or patients confined to pT1 stage.

The benefits of AC in rectal cancer patients who received preoperative CRT remain controversial (16, 31-36). In the ADORE phase 2 trial and the CAO/ARO/AIO-04 phase 3 trial of Stage II and III rectal cancer patients, oxaliplatin-based AC improved DFS (34, 35). However, Lu *et al*. have reported that AC using 5-FU with or without oxaliplatin provided no significant benefit for ypT0-2N0 rectal cancer by retrospectively analyzing 110 patients (37). Therefore, postoperative AC may not be necessary for rectal cancer patients with ypT1N0 stage. Consistent with this, no ypT1 patients had recurrence in our cohort, although only 6% received 5-FU-based AC. Collectively, further studies with a higher evidence level are required to confirm that AC has no impact on the survival of (y)pT1 rectal cancer.

The current study contains several other limitations due to its retrospective nature. The study contained only a small number of patients at a single center. As only three patients developed recurrence during the short follow-up period, there may have been type II errors in the identification of prognostic factors. In conclusion, the prognosis of patients with ypT1 rectal cancer did not differ from that of patients with pT1 rectal cancer in the current study. However, only low tumor location from the anal verge was a significant factor for a poor RFS.

Conflicts of Interest

The Authors declare that they have no conflicts of interest regarding this study.

Authors' Contributions

T.T. and H.N. contributed to the conception, design and acquisition of data. K.K., K.S., K.M., M.K., S.E., Y.I., H.I., Y.Y., H.A., H.S., and S.I. contributed to the analysis and interpretation of data. T.T. and H.N. contributed to drafting the article. K.K., K.S., K.M., M.K., S.E., Y.I., H.I., Y.Y., H.A., H.S., and S.I. contributed to revising it critically for significant intellectual content. All Authors approved the final version of this manuscript for publication.

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