Oncologic Outcome of ypT1-2N0 Rectal Cancer After Neoadjuvant Chemoradiotherapy Compared With pT1-2N0 Rectal Cancer

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Objective: To investigate the oncologic outcome of ypT1-2N0 mid and lower rectal cancer after chemoradiotherapy (CRT) compared with pT1-2N0 rectal cancer.

Methods: We compared the oncologic outcome of patients with mid and lower rectal cancer who underwent preoperative CRT and who did not, between February 2005 and August 2012.

Results: Compared with patients who did not receive preoperative CRT, patients who received preoperative CRT did not have significantly different clinicopathologic features except clinical stage and distal resection margin. The 5-year disease-free survival (DFS) rates were lower in patients who received preoperative CRT than those who did not (84.4% vs. 95.5%, $P = 0.029$). Preoperative CRT was a prognostic factor affecting 5-year DFS in patients with pathologically proven stage T1N0 mid and lower rectal cancer (HR, 11.157; 95% CI, 1.735-71.762; $P = 0.011$)

Conclusions: ypT2N0 rectal cancer after neoadjuvant CRT showed shorter DFS compared with pT2N0 rectal cancer.

Key Words: ypT1-2N0, prognosis, rectal cancer, chemoradiotherapy

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Preoperative chemoradiotherapy (CRT) has been widely accepted as a standard treatment for locally advanced mid and lower rectal cancer to improve local control of the disease.[1,2] The pathologic features of tumor may change after chemoradiation therapy, influencing the prognosis of rectal cancer. The tumor response to preoperative CRT is various, ranging from complete response to progression.

It remains to be determined which factors can predict the prognosis precisely in rectal cancer patients receiving preoperative CRT. Many studies have suggested that pathologic stage is more predictive of oncologic outcomes than clinical stage in rectal cancer patients receiving CRT.[3–6]

On the contrary, the standard treatment for T1-2N0 disease is surgery alone without preoperative or postoperative CRT.[7] Actually, pathologic T1-2N0 rectal cancer shows an excellent prognosis without preoperative chemoradiation therapy. However, the prognostic ability of pathologic T1-2N0 rectal cancer after neoadjuvant chemotherapy and radical surgery remains unclear and undetermined. Although it is well known that complete pathologic response to chemoradiation therapy is associated with good prognosis,[8–12] there are few studies assessing the oncologic outcome of patients with ypT1-2N0 rectal cancer who underwent preoperative chemoradiation therapy.[13] Therefore, it is necessary to assess whether patients with ypT1-2N0 rectal cancer show similar excellent prognosis compared with those with pT1-2N0 rectal cancer.

The aim of this study was to investigate the oncologic outcome in patients with ypT1-2N0 rectal cancer who underwent CRT and radical surgery and compare with those who did not receive preoperative CRT.

PATIENTS AND METHODS

We analyzed the prospectively collected data of patients with middle and lower rectal cancers who underwent preoperative CRT between February 2005 and August 2012 at our University Hospital. Inclusion criteria were patients with histologically proven primary adenocarcinoma of the middle and lower rectum. Patients with distant metastasis at diagnosis, synchronous malignancy, and a history of other malignant tumors within 5 years were excluded. A total of 103 consecutive patients were finally included in this study and divided into those with ypT1-2N0 (N = 25) and those with pT1-2N0 (N = 78). The study was approved by the institutional review board at our hospital.

The distance from the anal verge to the lower margin of the tumor was measured by rigid proctoscopy before the surgery. We defined lower rectal cancer as lesions located within 5 cm of the anal verge, whereas middle rectal cancer was defined as tumor located between 5 and 10 cm from the anal verge.

Preoperative staging was performed using colonoscopy, chest and abdominopelvic computed tomography (CT) scans, and pelvic MRI. Pretreatment biopsy sample was obtained endoscopically.

Preoperative radiotherapy was delivered to the pelvis 5 days per week for 5 weeks with a daily fraction of 1.8 Gy. A boost of 5.4 Gy was added to the tumor bed. During radiotherapy, concomitant chemotherapy was performed. Chemotherapy regimen was selected among 5-fluorouracil, capecitabine, or FOLFOX. Surgery was scheduled 4 to 6 weeks after completion of CRT. Pathologic staging was performed using the AJCC 7th criteria.

Patients were followed up every 3 months for the first 2 years after surgery, every 6 months for the next 3 years, and yearly thereafter. The follow-up examinations included physical examinations and serum carcinoembryonic antigen (CEA) assay. Chest x-ray, abdominopelvic CT, and colonoscopy were performed 6 months after operation and annually thereafter, as well as on suspicion of recurrence. Positron emission tomography was performed on suspicion of recurrence. The patients were followed up until death or the cut-off date (December 31, 2014). Median follow-up time was 62 months (range, 15 to 116 mo).

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Recurrence was diagnosed comprehensively by clinical findings, radiologic determinations, such as CT and positron emission tomography, and rise in the serum CEA level.

Statistics

Differences in stem cell marker expression and clinicopathologic variables were analyzed using Pearson χ^2 test and Fisher exact test. The association between survival and each parameter was assessed independently with a univariate logistic regression model. Parameters found to be potentially associated with survival, based on a P-value ≤ 0.2, were included in the multivariable model. A stepwise forward procedure was used to derive a final model of the variables that had a significant independent relationship with survival. The Kaplan-Meier method was used to calculate the survival rate. Differences between survival curves were analyzed by the log-rank test. Multivariate analysis was performed using the Cox regression model to study the effect of different variables on survival. The final multivariable model included the predictors with $P < 0.05$. The SPSS program for Windows version 13.0 (SPSS Inc., Chicago, IL) was used.

RESULTS

Clinicopathologic Characteristics

Of the 103 patients, 25 patients received preoperative CRT and 78 did not. Among those who underwent preoperative CRT, 19 (76%) patients received adjuvant chemotherapy. Among those who received adjuvant treatment, two patients developed recurrence, and among those who did not receive adjuvant treatment, one patient recurred. Patients and tumor characteristics are shown in Table 1. Sex, distal resection margin, number of retrieved LNs, and pretreatment CEA were significantly different between the 2 groups.

Recurrence Rate and Survival Analysis

The mean follow-up time was 65.6 months (range, 15 to 116 mo; median, 62 mo). Five patients had a recurrence. Recurrence rate was higher in patients who received preoperative CRT, but the significance was marginal ($P = 0.091$) (Table 2). The 5-year disease-free survival (DFS) rate was lower in patients who received preoperative CRT than those who did not (84.4% vs. 95.5%, $P = 0.029$). Subanalysis of pathologic T stage showed that the difference in DFS rate was mainly due to the difference between yT2 and T2 (81.8% vs. 97.4%, $P = 0.027$). However, there was no significant difference in 5-year overall survival between patients who did and did not receive preoperative CRT (94.1% vs. 95.1%, $P = 0.856$) (Fig. 1).

In univariate analysis, preoperative CRT was the only significant predictor for DFS. The sex, age, tumor location, tumor differentiation, pathologic T stage, lymphovascular invasion, distal resection margin, number of, retrieved LNs, and pretreatment CEA level had no significant influence on DFS (Table 3). Cox multivariate analysis demonstrated that preoperative CRT (HR, 11.157; 95% CI, 1.735-71.762; $P = 0.011$) and sex (HR, 9.512; 95% CI, 1.003-90.240; $P = 0.050$) were prognostic factors affecting 5-year DFS in patients with pathologically proven stage T1N0 mid and lower rectal cancer. Age, tumor location, histologic differentiation, pathologic T stage, lymphovascular invasion, distal resection margin number of, retrieved LNs, preoperative CEA level, and clinical stage were not independent prognostic factors.

TABLE 1. Clinicopathologic Characteristics of Patients

Variables	ypT1-2N0 n (%)	pT1-2N0 n (%)	*P*
Sex			0.007
Male	19 (76.0)	35 (44.9)	
Female	6 (24.0)	43 (55.1)	
Median age (range) (y)	55 (34-74)	58.5 (28-84)	0.317
Location			0.057
Mid	11 (44.0)	51 (65.4)	
Lower	14 (56.0)	27 (34.6)	
Tumor differentiation			0.050
Well	1 (4.0)	17 (21.8)	
Moderate	24 (96.0)	57 (73.1)	
Poor	0	4 (5.1)	
Clinical T and N stage			<0.001
cT1-2N0	0	60 (76.9)	
cT3-4N0	3 (12.0)	9 (11.5)	
cN+	22 (88.0)	9 (11.5)	
Pathologic T stage			0.061
T1	4 (16.0)	28 (35.9)	
T2	21 (84.0)	50 (64.1)	
Lymphovascular invasion			0.066
Negative	24 (96.0)	61 (78.2)	
Positive	1 (4.0)	17 (21.8)	
Distal resection margin (cm)	3 (1-7.5)	2 (0.3-7)	<0.001
Retrieved LN			0.018
<12	15 (60.0)	26 (33.3)	
≥12	10 (40.0)	52 (66.7)	
Initial CEA			0.023
≤5	18 (72.0)	71 (91.0)	
>5	7 (28.0)	7 (9.0)	
Preoperative CEA			0.811
≤5	23 (92.0)	71 (91.0)	
>5	2 (8.0)	7 (9.0)	

CEA indicates carcinoembryonic antigen.

DISCUSSION

Treatment for mid and lower rectal cancer depends on the extent of the rectal disease. Preoperative CRT has been widely accepted as a standard treatment for locally advanced rectal cancer (stage T3/T4 or node positive), whereas the standard treatment for T1-2N0 disease is surgery alone without preoperative or postoperative CRT.[7]

Initially, locally advanced rectal cancer can be downstaged, even until complete disappearance of the tumor with preoperative CRT. However, the impact of downstaging on prognosis still remains to be determined. It is well known that the complete tumor response to preoperative CRT is associated with an excellent prognosis.[8–12] In addition, patients with ypN0 rectal cancer are reported to show a better prognosis than those with lymph node-positive disease after receiving preoperative CRT.[3,4,14] However, there are a few studies

TABLE 2. Patterns of Recurrence

Recurrence	ypT1-2N0 n (%)	pT1-2N0 n (%)	*P*
Total	3 (12.0)	2 (2.6)	0.091
Local	0	1 (1.3)	
Distant	3 (12.0)	1 (1.3)	
Lung	3 (12.0)	1 (1.3)	

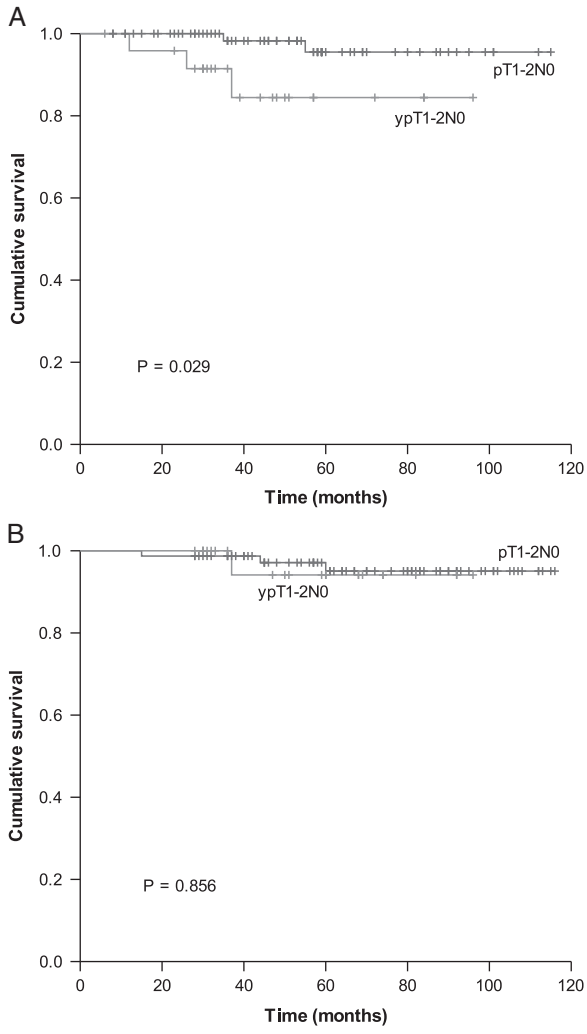

FIGURE 1. A, Comparison of 5-year disease-free survival rate between patients who underwent preoperative chemoradiotherapy and those who did not. B, Comparison of 5-year overall survival rate between patients who underwent preoperative chemoradiotherapy and those who did not.

comparing the prognosis between patients who underwent preoperative CRT and those who did not undergo preoperative CRT.

We analyzed the data to determine the recurrence pattern and oncologic outcomes of ypT1-2N0 rectal cancer, which was assessed as a tumor with radiologically regional lymph node metastasis and compared their features with those of pT1-2N0 rectal cancer. Essentially, the comparison between non-irradiated and radiated patients is unfair because irradiation can alter the pathologic features of the tumor. Although tumor location is not different between the 2 groups, the distal resection margin is longer in irradiated patients. It may be associated with tumor shrinkage that is caused by radiation effect. The number of retrieved LNs is lower in radiated patients compared with non-irradiated patients. This phenomenon is similar to that observed in previous studies.[15,16] It has been reported that the decreased number of retrieved LNs after CRT does not affect the prognosis.[17]

Our results showed that the recurrence rates of ypT1-2N0 and pT1-2N0 disease were 12.0% and 2.6%, respectively, although the recurrence rate of 3 versus 2 is too low. A previous study reported the recurrence rate of ypT0N0 and ypT1-2N0 disease as 2.7% and 12.3%, respectively, in patients who received preoperative CRT,[18] which is similar to our results. The recurrence rate of pT1N0 disease in this study was comparable to that of ypT0N0 disease in their study, although that study did not include patients with pT1-2N0 disease. Patients with ypT1-2N0 disease who received preoperative CRT are likely to have recurrence of the disease compared with those with pT1-2N0 disease who did not undergo CRT. Therefore, it is necessary to try to detect a recurrence rate more closely than true T1-2N0 disease.

Recurrence patterns were different between the 2 groups. Among those who received preoperative CRT, 3 patients (12.0%) developed a recurrence at distant site. All of them corresponded to T2 disease, representing 14.3% of the disease. These results are consistent with previous studies.[3,14] Das and colleagues showed that 5-year freedom from local recurrence and distant metastasis was 97% and 90%, respectively. Another study reported that the local and systemic recurrence rate was 1.9% and 9.7%, respectively, in ypT2N0 rectal cancer. Among those who received immediate surgery, one patient (1.4%) recurred at a local site and another patient (1.4%) recurred at a distant site. Nissan et al[19] reported that the local and distant recurrence rate was 7.4% and 24.5%, respectively, in patients with T2 and early T3 N0 rectal cancer treated by surgical resection alone. Du and colleagues showed that the local and distant recurrence rate was 4.4% and 13.3% in yp-stage I disease and 2.6% and 7.7% in p-stage I disease. We did not find a significant difference in the recurrence pattern between ypT1-2N0 disease after preoperative CRT and pT1-2N0 disease because of the paucity of data about pT1-2N0. In the future, it is necessary to compare the recurrence pattern between ypT1-2N0 disease and pT1-2N0 disease.

We found that DFS of patients with pathologic T1-2N0 disease after preoperative CRT is significantly different from that of patients with T1-2N0 disease proven after surgery alone. This result is contradictory to that in a previous study comparing rectal cancer patients who were confirmed as ypN0 disease after preoperative CRT and surgery with those with initial node-negative disease.[20] This discrepancy can be explained by the differences in inclusion criteria. They included patients with T1-4N0 disease in the control group, whereas we selected only patients with T1-2N0 disease for the control group because they do not need to receive preoperative CRT. There was only 1 study comparing primary and postirradiated rectal cancer with T1-2N0 disease similar to our study.[13] However, they reported that there was no significant difference in disease-free and overall survival between them. This discrepancy may be attributable to the inclusion of higher proportion of clinical stage III rectal cancers rather than clinical stage II diseases for preoperative chemotherapy in our study.

There were proportionally more T2 patients in the yp group, although it was not found to be statistically significant. Actually, ypT1 is very rare after combined CRT in the study. Subanalysis showed that survival rate was significantly different between yT2 and T2.

However, there was no difference between yT1 and T2. We found that the difference is significant between yT2 and T2.

On the contrary, we found no significant difference between patients with ypT1-2N0 disease and those with pT1-2N0 disease in terms of overall survival. This can be explained by the fact that most recurrent diseases had a single lesion and could be controlled by surgical resection.

Several studies investigated the role of adjuvant chemotherapy in patients showing a good prognosis who underwent

TABLE 3. Univariate Analysis of Survival Among Patients With Pathologically Proven T1-2N0 Disease

Variables	N	5 y DFS	*P*	5 y OS	*P*
Sex			0.118		0.052
Male	54	97.3		90.4	
Female	49	87.6		100	
Age (y)			0.589		0.007
< 65	66	91.8		100	
≥ 65	37	95.5		86.1	
Location			0.452		0.763
Mid	62	93.3		96.2	
Lower	41	91.7		93.6	
Tumor differentiation			0.350		0.847
Well	18	78.1		92.9	
Moderate	81	95.0		95.3	
Poor	4	100		100	
Clinical T and N stage			0.741		0.690
cT1-2N0	61	93.2		93.3	
cT2-4N0	11	90.9		100	
cN+	31	91.4		95.7	
Pathologic T stage			0.725		0.845
T1	32	88.9		95.7	
T2	71	93.1		94.7	
LV invasion			0.266		0.326
Negative	85	90.9		93.8	
Positive	18	100		100	
Distal resection margin (cm)			0.806		0.421
< 1	14	87.5		100	
≥ 1	89	94.1		94.2	
Retrieved LN			0.205		0.103
< 12	41	89.9		89.2	
≥ 12	62	94.8		98.0	
Initial CEA			0.716		0.309
≤ 5	89	93.2		96.9	
> 5	14	90.0		90.9	
Preoperative CRT			0.029		0.856
No	78	95.5		95.1	
Yes	25	84.4		94.1	

CEA indicates carcinoembryonic antigen; CRT, chemoradiotherapy; DFS, disease-free survival; OS, overall survival.

neoadjuvant CRT.[3,21,22] The prognostic value of postoperative chemotherapy in patients showing good responses remains unclear. Our study showed that 19 (76%) of patients who underwent preoperative CRT received adjuvant chemotherapy. Two recurred among patients who received adjuvant treatment, and 1 recurred among patients who did not. We could not compare patients who underwent postoperative chemotherapy and those who did not because the sample size was small and most patients underwent postoperative chemotherapy. The role of adjuvant chemotherapy after neoadjuvant chemotherapy remains unclear, although there are randomized trials showing no benefit of 5-fluorouracil-based adjuvant chemotherapy.[23]

This retrospective study has a few limitations. First, the number of patients is too small to provide adequate power for drawing any definitive conclusions regarding oncologic outcomes. Second, a single-institution retrospective analysis has an inherent selection bias. Third, there is an inherent drawback in this study. Some patients who received preoperative CRT might have been overtreated because the current preoperative imaging staging is insufficient,[24,25] although MRI is recommended to stage rectal cancer for making a treatment decision. Nonetheless, we suggest that rectal cancer which proves to be pT1-2N0 disease after preoperative CRT should be considered a different disease from true T1-2N0 disease in rectal cancer.

CONCLUSIONS

This study suggests that patients with ypT2N0 rectal cancer who received preoperative CRT showed shorter DFS compared with those with pT2N0 rectal cancer. However, further studies including a large sample size are warranted to determine the prognostic value of ypT1-2N0 rectal cancer and to establish the prognostic factors.

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