The impact of the radiation-induced regression of positive nodes on survival in patients with rectal cancer treated with chemoradiotherapy

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Background. *Although preoperative chemoradiotherapy exerts a destructive effect on positive lymph nodes, microscopic examination reveals different degrees of tumor regression. The aim of the present study is to investigate the impact of the radiation-induced regression of positive nodes on survival in patients with rectal cancer treated with preoperative chemoradiotherapy.*

Methods. *From 2001 to 2015, 229 patients with T3 rectal cancer underwent total mesorectal excision after preoperative chemoradiotherapy. The patients were classified into 3 groups according to their lymph node status: residual cancer cells in positive nodes (Group A), total regression of positive nodes after preoperative chemoradiotherapy with complete fibrosis (Group B), and the entire lymph node filled with lymph nodules and the absence of fibrosis (Group C). The survival of the 3 groups was compared, and a Cox model was used to evaluate the prognostic value of the regression of the positive nodes by preoperative chemoradiotherapy.*

Results. *Groups A, B, and C included 57, 18, and 154 patients, respectively. Group B showed significantly better overall survival than Group A (*P = *.041) and similar outcomes to Group C (*P = *.383). Among the patients with positive lymph nodes prior to treatment (Groups A and B), the total regression of the positive nodes after preoperative chemoradiotherapy was the only independent factor to be associated with good overall survival (hazard ratio; 6.26, 95% confidence interval; 1.28–113.0,* P = *.020).*

Conclusion. *Total regression of positive nodes by preoperative chemoradiotherapy improves the prognosis of patients with rectal cancer with positive lymph nodes prior to treatment. (Surgery 2017;161:422-32.)*

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Preoperative chemoradiotherapy (CRT) is a widely accepted treatment for locally advanced rectal cancer due to its ability to achieve tumor downstaging and its subsequent improvement in control of local disease.[1-3] In contrast, preoperative CRT also has a destructive effect on positive lymph nodes, and the rate of node metastasis is decreased from approximately 60% to 30% in patients with T3 or T4 rectal cancer.[4-7] Thus, approximately half of pretreatment N+ patients become ypN0 after preoperative CRT.

Although the other 30% of patients have positive nodes, these nodes demonstrate different degrees of tumor regression. Cancer cells in nodes can be decreased by preoperative CRT resulting in fibrosis, or cancer cells can disappear completely and a fibrotic response may not occur (Fig 1, *A–D*). As a result, the different oncologic outcomes may be related to the degree of tumor regression of positive nodes. Thus, the aim of the present study

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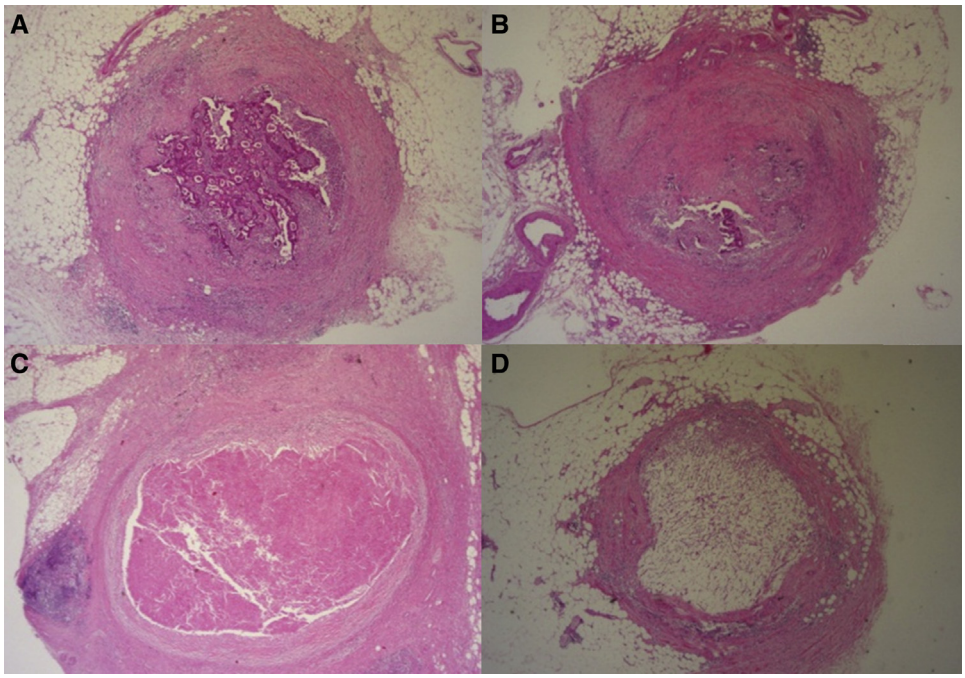


Fig 1. The regression process of clinically positive nodes treated with preoperative CRT. (*A*) Fibrosis with cancer cells or no fibrosis with extensive residual cancer cells. (*B*) Residual cancer cells with associated fibrosis. (*C*) No cancer cells with associated fibrosis. (*D*) No cancer cells with no fibrosis evident. (Color version of this figure is available online.)

was to investigate the impact of the radiation-induced regression of positive lymph nodes on the survival of patients with rectal cancer who undergo preoperative CRT.

MATERIALS AND METHODS

Patients. The present study included consecutive patients with rectal cancer who were treated between 2001 and 2015. Our strategy for rectal cancer was as follows: clinical T1 and T2 rectal cancer was treated by primary operation without preoperative therapy; clinical T3 rectal cancer was treated by total mesorectal excision (TME) after short-course radiotherapy with delayed surgery (SRT-delay); and patients with clinical T4 rectal cancer, or patients with lateral lymph node involvement (defined by nodes of >8 mm in size) were treated by long-course chemoradiotherapy, because the effects of the SRT-delay approach have not been confirmed in patients with highly advanced rectal cancer.[8-10]

During the study period, we treated a total of 273 patients with T3 rectal cancer with a histopathologically confirmed diagnosis of adenocarcinoma. We excluded 24 patients with synchronous metastases and 20 patients with lateral lymph node involvement of >8 mm. The remaining 229 patients who underwent curative resection after SRT-delay were included in this study (Tables I and II). Prior to SRT-delay, all of the patients underwent staging, which included a digital rectal examination, measurement of the serum tumor marker levels (CEA and CA19-9), chest radiography, abdominal and pelvic computed tomography (CT), magnetic resonance imaging, and colonoscopy with biopsy.

Treatment. All of the patients received the SRT-delay regimen. The details of this regimen have been described previously.[8-10] Our SRT-delay regimen was modified in 2 ways: we adopted fractionated radiotherapy and used a chemoradiosensitizer. A total dose of 25 Gy was administered in 10 fractions of 2.5 Gy each over a period of 5 days. Radiotherapy was performed using the radiosensitizer, S-1 (60 mg/m^2/day; Taiho Pharmaceutical Co, Tokyo, Japan), for 10 continuous days from the start of radiotherapy.

The field margins of each beam were defined as follows: the cranial margins were the anterior iliac crests or the L4–5 interspace, the caudal margins were the ischial tuberosities, the lateral margins were expanded 1.5 cm beyond the sacroiliac joint, the anterior margins were the dorsal edge of the pubic joint, and the posterior field margins were designed to include the posterior edge of the sacrum. The target interval between the completion of radiotherapy and operation was 4 weeks. After the completion of the SRT-delay regimen, all patients underwent curative resection with TME.

Table I. The characteristics of the patients with rectal cancer who underwent preoperative CRT

	Total (n = *229*)	*Groups A and B* (n = *75*)	*Group C* (n = *154*)	P *value*	*Odds ratio*	*95% confidence interval*	P *value*
Age (y)							
≤64	117	34	83				
>65	112	41	71	.224			
Sex							
Male	156	52	104				
Female	73	23	50	.784			
Clinical T3	229	75	154				
Clinical N							
Negative	88	22	66				
Positive	141	53	88	.048	1.48	0.620–5.03	.657
M0	229	75	154				
Type of operation							
Sphincter preservation	204	68	136				
Permanent stoma	25	7	18	.592			
ypT							
0–2	100	16	84				
3,4	129	59	70	≤.001	5.16	2.54–11.29	<.001
(ypT0)	(19)	(3)	(16)				
pCR	16	0	16				
CRM							
Negative	215	68	147				
Positive	14	7	7	.156			
Differentiation							
Differentiated type	210	68	142				
Nondifferentiated type	19	7	12	.692			
Lymphvascular invasion							
Negative	162	35	127				
Positive	67	40	27	≤.001	4.89	2.12–9.78	<.001
Perineural invasion							
Negative	167	48	119				
Positive	62	27	35	.034	1.61	0.78–4.29	.412
TRG							
1a,1b	139	50	89				
2,3	90	25	65	.197			
Adjuvant chemotherapy							
No	51	20	31				
Yes	178	55	123	.265			

pCR, Pathologic complete response; *CRM*, circumferential resection margin; *TRG*, tumor regression grade.

The pathologic findings. In the pathologic examination of the resected specimens, we followed the Japanese Clinical and Pathological Guidelines for the Colon, Rectum and Anus 7th edition.[11] As described previously,[12,13] this can be summarized as follows: the lymph nodes were harvested by palpation and fresh specimens were inspected visually without the use of a cleaning solution. After the harvesting of the lymph nodes, the operative specimens were fixed in 10% buffered neutral formalin for approximately 24–48 hs. After fixation, formalin-fixed lymph nodes were cut subsequently at 2-mm intervals along the largest diameter to obtain the maximum size. The tissue was embedded in paraffin, sliced at a thickness of 3 μm, and stained with hematoxylin and eosin.

We classified the patients into 3 groups (Groups A–C) according to their microscopic findings: residual cancer cells in the positive nodes (Group A), total regression of the positive nodes after preoperative CRT and complete fibrosis (Group B), and the entire lymph node filled with lymph nodules with absence of any fibrosis (Group C) (Table III). Clinically, Group A (residual cancer cells in lymph nodes) patients are N+ and show radioresistance at the pretreatment phase and no N stage migration after preoperative CRT. In contrast, Group B (only fibrosis and no

Table II. The characteristics of patients with rectal cancer with pathologically confirmed pretreatment N+ who underwent preoperative CRT

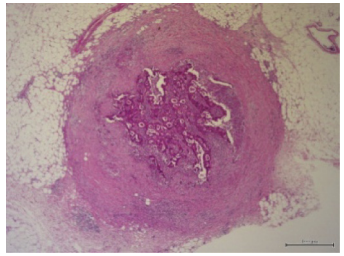
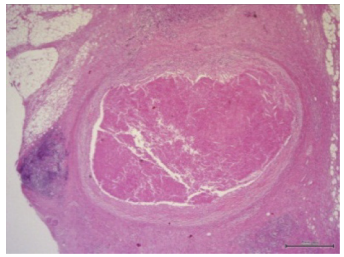
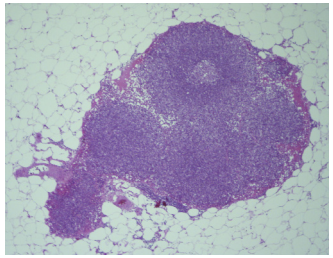
	Group A (n = *57*)	*Group B* (n = *18*)	P *value*	*Odds ratio*	*95% confidence interval*	P *value*
Age (y)						
≤64	28	6				
>65	29	12	.241			
Sex						
Male	40	12				
Female	17	6	.778			
Clinical T3	57	18				
Clinical N						
Negative	16	6				
Positive	41	12	.669			
M0	57	18				
Type of operation						
Sphincter preservation	53	15				
Permanent stoma	4	3	.220			
ypT						
0–2	7	9				
3,4	50	9	<.001	7.14	2.15–25.24	.013
(ypT0)	2	1				
Number of positive nodes*						
1	20	14				
2	16	4				
3	6	0				
4+	15	0				
CRM						
Negative	52	16				
Positive	5	2	.211			
Differentiation						
Differentiated type	52	16				
Nondifferentiated type	5	2	.766			
Lymphovascular invasion						
Negative	25	10				
Positive	32	8	.386			
Perineural invasion						
Negative	36	12				
Positive	21	6	.787			
TRG						
1a,1b	40	10				
2,3	17	8	.251			
Adjuvant chemotherapy						
No	15	5				
Yes	42	13	.902			

*The number of positive nodes was not entered into the statistical analysis.
CRM, Circumferential resection margin; *TRG*, tumor regression grade.

residual cancer cells in the lymph nodes) patients are radiosensitive at the pretreatment phase and show N stage migration to ypN0 after preoperative CRT.

Therefore, Groups A and B were confirmed pathologically to have N+ rectal cancer prior to treatment, because the specimens contained cancer cells and/or fibrosis. In contrast, Group C included 2 subgroups: pretreatment N0 patients and radiosensitive pretreatment N+ patients with the stage migration to ypN0 after preoperative CRT; however, the 2 groups could not be distinguished based on the microscopic findings, because the positive nodes showed complete degeneration after preoperative CRT and no scarring of positive nodes was confirmed in the pretreatment N+ patients of Group C. The National Comprehensive Cancer Network and The

Table III. Examples and definitions of the lymph node statuses

Classification	*Lymph node status*	*ypN staging*	*Examples*	*Definition*
Group A	Pathologically confirmed pretreatment N+ rectal cancer	ypN+		Residual cancer cells in positive nodes.
Group B		ypN0		The total regression of positive nodes after preoperative CRT and complete fibrosis.
Group C				Entire lymph node filled with lymph nodules and the absence of fibrosis.

European Society for Medical Oncology guidelines both classify Groups B and C as ypN0 due to the lack of residual cancer cells in their lymph nodes; Group A is classified as ypN+.[14,15]

Radio-response of primary tumor was assessed by the tumor regression grade (TRG) which was classified into 5 histologic tumor regression grades based on vital tumor tissue of the ratio of fibrosis[11]: Grade 0 was defined as No evidence of effect; Grade 1a was defined as viable tumor cells occupying more than two thirds; Grade 1b was defined as viable tumor cells remaining in more than one third but less than two thirds of the tumorous area; Grade 2 was defined as viable tumor cells remaining in less than one third of the tumorous area; and Grade 3 (complete response [CR]) was defined as no viable tumor cells remaining.

The histopathologic characteristics of the tumor and the response to preoperative CRT were evaluated by 3 gastrointestinal pathologists (SH, TN, or NT), and 1 gastrointestinal pathologist (AK) confirmed that the diagnosis of the 3 gastrointestinal pathologists was consistent for all specimens.

Patient follow-up. The median follow-up period was 55 mo (range, 1–163 mo). Adjuvant, oral, 5FU-based chemotherapy was recommended in all patients after resection. Patient surveillance was performed as follows: a chest-abdominal CT was performed every 6 months, colonoscopy was performed annually, and blood tests (including the measurement of the serum CEA and CA 19-9 levels) were performed at 3-month intervals. Local recurrence was defined as the detection of a recurrent tumor within the pelvis and systemic recurrence as the presence of recurrent disease outside the pelvis.

Statistical analysis. The χ^2 test was used for the univariate analyses. All variables with a P value of $<.10$ were entered into a multiple logistic regression model. Local recurrence-free survival (LFS), recurrence-free survival (RFS), and overall survival (OS) were calculated using the Kaplan-Meier method, and differences were evaluated using a log-rank test. A multivariable analysis was performed using the Cox proportional hazards model. The analysis included variables that were identified as being associated with recurrence and survival in the univariate analysis. The data were analyzed using the JMP 10.0 software program (SAS Institute Inc, Cary, NC).

RESULTS

Patient characteristics. The characteristics of the 229 patients in the study population are summarized in Table I. A total of 75 patients were classified into Groups A and B based on the presence of pathologically confirmed pretreatment N+ rectal cancer, while 154 patients were classified into Group C based on the observation of a lymph node filled with lymph nodules. The median age was 63.0 years (range: 35–85 years), and the primary tumor was located at 4.8 ± 2.1 cm (range, 0–8 cm) from the anal verge.

A total of 178 patients (77.7%) received adjuvant chemotherapy after resection. The reasons for not receiving chemotherapy included: advanced age or the presence of comorbidities ($n = 28$), postoperative complications ($n = 13$), and other reasons ($n = 10$). The differences between the combination of Groups A and B and Group C that were identified in the univariate analysis were as follows: clinical N ($P = .048$), ypT ($P < .001$), lymphovascular invasion ($P < .001$), and perineural invasion ($P = .034$). The ypT (odds ratio [OR], 5.16; 95% confidence interval [95%CI], 2.54–11.29; $P < .001$) and lymphovascular invasion (OR, 4.89; 95% CI, 2.12–9.78; $P < .001$) were confirmed to be significant factors in the multivariate analysis.

Of 75 patients with pathologically confirmed, pretreatment, N+ rectal cancer, residual cancer cells in positive nodes were observed in 57 patients (Group A) and total regression of positive nodes were observed in 18 patients (Group B). Total regression in only 1 positive node and 2 positive nodes were observed in 14 and 4 patients of Group B, respectively.

Among the patients with pathologically confirmed, N+ rectal cancer, significant differences between residual cancer cells in positive nodes and total regression of positive nodes were observed ypT classification ($P < .001$) in both the univariate analysis and multivariate analysis (OR, 7.14; 95% CI, 2.15–25.24; $P = .013$).

Five-year LFS, RFS, and OS. The 5-year LFS, RFS, and OS rates among Groups A, B, and C were 86%, 92%, and 94%; 55%, 87%, and 86%; and 66%, 93%, and 89%, respectively (Fig 2). The RFS and OS of Group B was better than that observed in Group A (RFS; $P = .028$, OS; $P = .041$). The outcome in Group B was similar to that observed in Group C (RFS; $P = .818$ and OS; $P = .383$).

The influence of different covariables on 5-year LFS, RFS, and OS in patients with rectal cancer with pathologically confirmed pretreatment N+ who underwent preoperative CRT. We examined the prognostic significance of various clinicopathologic factors among the patients with rectal cancer with pathologically confirmed pretreatment N+

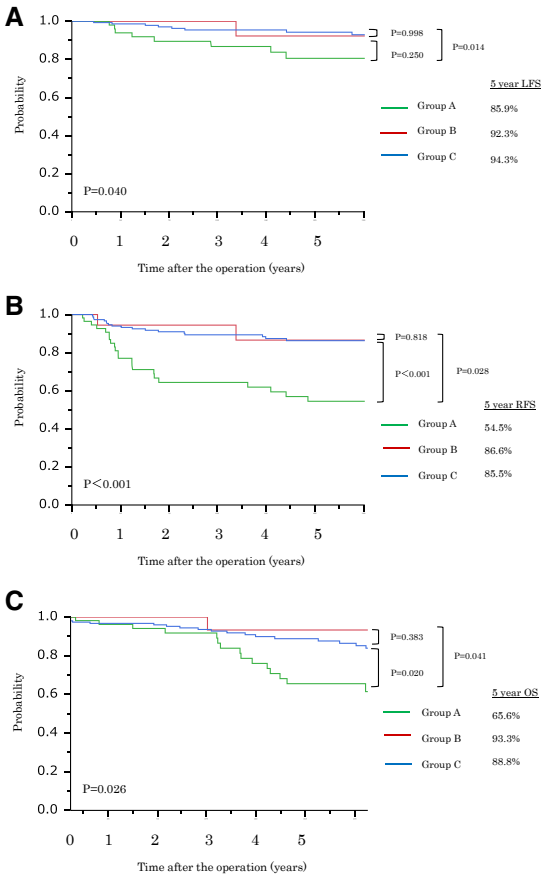


Fig 2. The 5-year LFS, RFS, and OS for patients with rectal cancer who underwent preoperative CRT stratified by lymph node status. (*A*) *LFS*, Local recurrence-free survival. (*B*) *RFS*, recurrence-free survival. (*C*) *OS*, overall survival. (Color version of this figure is available online.)

(Groups A and B) using univariate and multivariate analyses (Tables IV and V). Overall, the 5 year LFS, RFS, and OS were 84%, 62%, and 72%, respectively. The univariate analysis revealed significant associations between a positive circumferential resection margin and poor LFS (P = .011) and ypN+ and poor RFS and OS (P = .028 and P = .042, respectively); the association between the circumferential resection margin and poor LFS did not remain in the multivariate analysis (HR, 5.99; 95% CI, 0.89–25.1; P = .063).

The only independent prognostic factor identified by a multivariate analysis was the total regression of positive nodes after preoperative CRT, which was associated with good RFS (HR, 4.24; 95% CI, 1.24–26.5; P = .018) and OS (HR, 6.26; 95% CI, 1.28–113.0; P = .020). These findings suggest that good oncologic outcomes can be expected in patients with rectal cancer with pathologically confirmed node positivity when the total regression of positive lymph nodes is observed after preoperative CRT.

DISCUSSION

Preoperative CRT can achieve local control in patients with rectal cancer; however, the response of the primary tumor is associated with RFS and OS, and favorable outcomes can be expected in patients with total or major regression of the primary tumor.[16-21] In contrast, whether the patient is ypN0 or ypN+ after preoperative CRT is another important factor in predicting RFS and OS, because the prognosis of ypN+ patients is poor.[22-25]

With regard to the microscopic findings in ypN+ patients, however, nodes that are positive after preoperative CRT demonstrate various degrees of tumor regression: some ypN+ patients have a few residual cancer cells remaining in their positive nodes, while others have large numbers of residual cancer cells. Previous reports have demonstrated that the prognosis of all ypN+ patients is considered to be poor prognosis regardless of the number of residual cancer cells in their positive nodes.[22-25]

To solve this question, this study investigated the oncologic outcomes according to the degree of tumor regression in the clinically positive nodes. The results revealed that favorable outcomes could be expected in the patients with a total regression of positive nodes after preoperative CRT. Conversely, the prognosis of the patients with only minor regression was poor. Thus, the degree of destruction of the positive nodes by preoperative CRT is associated with the oncologic outcomes. It is a well-known fact that favorable outcomes can be expected in some patients with pathologic CR (pCR) of the primary tumor after preoperative CRT.[16-21] This phenomenon also applies to the positive nodes, and good oncologic outcomes can be expected in patients with rectal cancer with the total regression of positive nodes after preoperative CRT, even if they are N+ before treatment.

Consequently, based on the microscopic findings, the patients in Groups B and C were quite different, despite their TNM stage (ypN0) being the same due to the lack of any residual cancer cells in the lymph nodes (Table III). In the TNM system, the N stage is determined based on the presence or absence of cancer cells in the lymph nodes; however, our results demonstrated that the oncologic outcomes of Groups B and C were similar and that, from the viewpoint of survival, it

Table IV. The influence of different covariables on 5-year LFS, RFS, and OS in patients with rectal cancer with pathologically confirmed pretreatment N+ who underwent preoperative CRT

	No. at risk	*5-y LFS (%)*	P *value*	*5-y RFS (%)*	P *value*	*5-y OS (%)*	P *value*
Overall		83.6		62.3		72.2	
Median age (y)							
≤64	34	85.1		69.4		73.8	
64	41	82.6	.837	55.8	.329	70.9	.993
Sex							
Male	52	83.4		66.3		75.2	
Female	23	83.1	.867	52.6	.139	66.3	.767
Type of operation							
Sphincter preservation	68	85.0		62.6		74.4	
Permanent stoma	7	68.6	.133	57.1	.553	53.6	.378
ypT stage							
0–2	16	87.5		64.6		73.0	
3,4	59	82.4	.495	53.9	.533	67.5	.862
ypN status							
Total regression of positive nodes	18	92.3		86.6		93.3	
Residual cancer cells in positive nodes	57	80.6	.250	54.5	.028	65.6	.042
CRM							
Negative	68	86.1		63.1		74.6	
Positive	7	50.0	.011	50.0	.382	33.3	.353
Differentiation							
Differentiated	68	82.9		61.9		71.8	
Nondifferentiated	7	87.5	.948	62.5	.742	72.9	.803
Lymphovascular invasion							
Negative	35	87.6		68.1		75.4	
Positive	40	74.3	.298	54.3	.174	65.3	.213
Perineural invasion							
Negative	48	88.5		70.3		78.3	
Positive	27	71.3	.224	52.1	.121	63.2	.157
Tumor regression grade							
1a,1b	50	82.2		57.1		67.3	
2,3	25	87.1	.380	71.7	.217	80.3	.442
Adjuvant chemotherapy							
No	20	81.9		61.3		71.6	
Yes	55	84.2	.754	65.1	.298	74.7	.741

CRM, Circumferential resection margin; *LFS*, local recurrence-free survival; *OS*, overall survival; *RFS*, recurrence-free survival.

Table V. The multivariate analysis of the different covariables associated with 5-year LFS, RFS, and OS among patients with rectal cancer with pathologically confirmed pretreatment N+ who underwent preoperative CRT

Significant variables in the univariate analysis	*5-y LFS*			*5-y RFS*			*5-y OS*		
	HR	*95% CI*	P	*HR*	*95% CI*	P	*HR*	*95% CI*	P
CRM	5.99	0.89–25.1	.063						
ypN status				4.24	1.24–26.5	.018	6.26	1.28–113.0	.020

CRM, Circumferential resection margin; *LFS*, local recurrence-free survival; *OS*, overall survival; *RFS*, recurrence-free survival.

was reasonable to classify both groups of patients as ypN0.

Park et al[26] demonstrated that among patients with radiosensitive rectal cancer in whom the T stage was decreased (ypT0–2), the oncologic outcomes of ypN+ patients with rectal cancer were not significantly worse than those of ypN0 patients. In contrast, among patients with radioresistant

rectal cancer in whom the T stage was not decreased (ypT3,4), the prognosis of ypN+ patients was significantly poorer than that of ypN0 patients.

These results suggest that the implications of ypN+ differed depending on whether or not T downstaging was achieved. The present study demonstrated that good oncologic outcomes could be expected even in patients who were N+ prior to treatment if the total regression of the clinically positive nodes was achieved (Group B) (Tables IV and V; Fig 2), and that a good level of regression in the positive nodes was associated strongly with T downstaging (Table II).

This study discussed the outcomes of patients in whom the total regression of positive nodes was achieved by preoperative CRT; however, good tumor regression might be achieved in patients whose disease is radiosensitive and in whom T downstaging is achieved if they have residual cancer cells in their positive nodes (ypT0–2). Consequently, the outcomes of the ypN0 and ypN+ patients did not differ. In contrast, in patients with radioresistant disease in whom T downstaging was not achieved (ypT3–4), the degree of regression in the positive nodes was minor. As a result, the outcomes of ypN+ patients were poor in comparison to the ypN0 patients.

Bujko et al[22] also described the association between a poor pathologic response of clinically positive nodes to preoperative CRT and a high risk of distant metastasis. Many reports have noted that the prognosis of all ypN+ patients is considered to be poor.[22-25] However, the subdivision of the ypN+ patient group based on clinicopathologic factors (T downstaging, etc) might allow the oncologic outcomes of ypN+ patients with rectal cancer to be more accurately predicted.

Group A, which comprised patients with residual cancer cells in positive nodes, had an extremely poor prognosis, and it is necessary to examine the current treatment strategies to improve the outcomes. The role of adjuvant chemotherapy after preoperative CRT is controversial and has not been formally proven.[27-29] Therefore, the routine use of adjuvant chemotherapy is not recommended, and a method of selecting patients who can be expected to respond well to adjuvant chemotherapy is needed.

To this end, the Adjuvant Oxaliplatin in Rectal Cancer (ADORE) trial evaluated patients with high-risk rectal cancer assigned randomly to receive preoperative CRT (ypT3–4 or ypN+) with either fluorouracil/leucovorin or FOLFOX and demonstrated the benefits of adding oxaliplatin.[30] The patients in this study were classified into 3 groups (A, B, and C) according to their lymph node status, and Group A (ypN+) patients were the most frequently recommended to receive adjuvant chemotherapy based on the results of the ADORE trial. In contrast, Group B and C patients were diagnosed to have a ypN0 status and thus were not recommended routinely to receive adjuvant chemotherapy.

Our study has several potential limitations. First, the study was retrospective in nature and included a limited number of patients, the most important being the few number of patients included. After the exclusion of cases for diverse reasons, only 75 patients were included, of whom only 18 had total tumor regression. The association between a poor pathologic response of the positive nodes to preoperative CRT and a high risk of distant metastasis has been proposed,[22,26] and our study supported this proposal pathologically.

Second, the best waiting period for 25Gy short-course radiotherapy has not been determined, and some trials have investigated the short-term and long-term outcomes of delayed resection of the primary neoplasm.[8,31-34] Among the patients who underwent the standard short-course regimen, the ypN status did not reflect the oncologic outcomes, and the ypN+ patient group included patients with both radiosensitive and radioresistant disease, because the interval between radiotherapy and resection was too short for necrosis to occur in the patients with radiosensitive disease.[22]

Our results demonstrated that even with 25 Gy of low-dose radiotherapy, a longer waiting period may allow for radiosensitive and radioresistant positive nodes to be distinguished. Although the SRT-delay regimen is still an exploratory regimen, the effects of preoperative CRT on the positive nodes could be clarified by varying the radiation dose (low or high dose) and/or the waiting period (immediate or delayed resection).

Finally, the main outcome of this study was the oncologic outcomes of the patients with the total regression of positive nodes (Group B); however, the number of Group B patients was limited, and further studies will be needed to confirm the findings.

In conclusion, good oncologic outcomes can be expected in patients with the total regression of positive nodes after preoperative CRT. Conversely, the prognosis of patients with minor regression of positive nodes was poor. The degree of regression of the positive nodes by preoperative CRT is, therefore, associated with the oncologic outcomes. This observation may prove

useful when considering the impact of the radiation-induced regression of positive nodes on survival in patients with rectal cancer treated with preoperative CRT.

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