Poorer Oncologic Outcome of Good Responders to PCRT With Remnant Lymph Nodes Defies the Oncologic Paradox in Patients With Rectal Cancer

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Abstract

Prognostic impact of metastatic lymph nodes should be carefully considered in deciding treatment plan after preoperative chemoradiotherapy (PCRT). The decision to withhold patients from complete local control by total mesorectal excision after PCRT needs to be made with caution: nodal positivity, not readily detectable with tools currently used in clinical staging, could be more lethal than it was previously believed in patients with rectal cancer that have not undergone PCRT.

Introduction: We evaluated the oncologic outcome of (y)pT0-2N+ rectal cancer and investigated the impact of metastatic lymph nodes (LNs) on oncologic outcome in the setting of preoperative chemoradiotherapy (PCRT). **Materials and Methods:** The records of 1403 patients who underwent surgery for rectal cancer between January 2005 and December 2012 were analyzed. The patients were categorized according to the pathologic stage, including 728 patients with ypT0-2 and 675 with ypT3-4 disease. The oncologic outcomes in terms of the 5-year recurrence-free survival (RFS) and overall survival (OS) were analyzed. **Results:** Metastatic LNs were observed in 11.5% (n = 84) of patients with ypT0-2 and 42.9% (n = 290) of patients with ypT3-4 disease. The RFS and OS were stratified according to ypT and ypN stage as ypT0-2N0, T0-2N+, T3-4N0, and T3-4N+. The ypT0-2N+ group had slightly lower RFS and OS than those in the ypT3-4N0 group. LN metastasis was significantly associated with RFS in both ypT0-2 and ypT3-4 disease, with a stronger association for ypT0-2 disease (hazard ratio, 3.473, 95% confidence interval, 2.058-5.261; $P < .001$ for ypT0-2 and hazard ratio, 2.038; 95% confidence interval, 1.601-2.684; $P < .001$ for ypT3-4, respectively). **Conclusion:** The oncologic outcomes of ypT0-2N+ disease were not favorable compared with those of ypT3-4N0 disease. These outcomes dispute the survival paradox traditionally believed for non-PCRT-treated patients with rectal cancer, and highlight the underestimated significance of post-PCRT nodal involvement. The prognostic importance of metastatic LNs should be considered when deciding the surgical strategy after PCRT. Further studies including larger numbers of patients with sufficient follow-up are needed to verify the oncologic impact of metastatic LNs within tumors contained within the bowel wall after PCRT.

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Keywords: Lymph node metastasis, Overall survival, Preoperative chemoradiotherapy, Recurrence-free survival Watch-and-wait

Introduction

There have been studies reporting survival paradox among patients with colorectal cancer in which those with cancer confined within the bowel wall but with metastatic lymph nodes (LNs) in the mesorectum, despite being staged higher, have better oncologic outcome than that of patients with tumors that infiltrate the bowel

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wall but without metastatic LNs,[1,2] although the American Joint Committee on Cancer (AJCC) staging system is the one of the most powerful prognostication measurements. With the advent and wide application of preoperative chemoradiotherapy (PCRT) for locally advanced rectal cancer, it remains unclear whether the same weight should be placed on pathologic LN metastasis in predicting the prognosis of patients who receive PCRT.

Organ-preserving strategies or deferral of surgery for patients with a good response to PCRT is becoming increasingly popular, yet up to 30% of rectal cancers clinically evaluated to have achieved complete regression after PCRT still harbor metastasized mesorectal LNs when total mesorectal excision (TME) is performed.[3,4] Thus, the overall prognosis of, and specifically, the impact of remnant metastatic LNs on patients who have received PCRT, is currently of utmost interest to surgeons and oncologists.

In this study, we delineated the prognosis of patients with rectal cancer who received PCRT followed by radical resection and determined the extent of impact of remnant metastatic LNs in patients whose cancers were contained within the rectal wall after PCRT.

Materials and Methods

Study Population

Our study included 1403 patients with mid and low rectal cancer initially evaluated to be in stages II or III, treated with PCRT, followed by radical resection between January 2005 and December 2012 at the Asan Medical Center of Seoul, Korea. Patients whose pathology results were unavailable or who were lost to follow-up were excluded. Patients who received local excision were also excluded. Among the remaining patients, those with synchronous metastatic disease were also excluded from analysis. This study was approved by the Institutional Review Board of Asan Medical Center (Registration no: 2017−1022).

PCRT and Surgical Resection

All patients received PCRT according to the treatment protocols of Asan Medical Center. Patients received 22 to 25 fractions of local irradiation to the pelvis, each 1.8 to 2.0 Gy, 5 times weekly for 5 weeks, resulting in a total of 44 to 45 Gy. Selected patients received a boost dose of radiation of 5.4 to 6.0 Gy to the primary tumor over 3 days, resulting in a total irradiation dose of 50 to 50.4 Gy. The primary tumor, perirectal adipose tissue, obturator, internal iliac, and presacral nodes were included in the clinical target volume. The superior border of the clinical target volume was the lower margin of the L5 spine, and the inferior border was 2 cm distal to the primary tumor.

All patients also received a concurrent chemotherapy regimen consisting of either an oral administration of capecitabine (825 mg/m^2) twice daily or 2 cycles of an intravenous bolus injection of 5-fluorouracil (375 mg/m^2/day) and leucovorin (20 mg/m^2/day) for 3 days during the first and fifth weeks of radiotherapy. As a part of a clinical trial, some patients received titanium silicate combined with oxaliplatin as an alternative first-line chemotherapy regimen. In these patients, titanium silicate was administered on days 1 to 28 every 42 days for 4 courses.

All patients were re-examined 4 to 6 weeks after completion of PCRT by physical examination, rectal magnetic resonance imaging (MRI), and sigmoidoscopy. Either a 1.5T or 3.0T scanner (MAGNETOM Avanto and Skyra; Siemens Medical Solutions, Erlangen, Germany) was used for the MRI scan. Evaluation with the mrTRG (MRI Tumor Regression Grade)[5] system was started in 2010 and applied to all patients after PCRT before radical resection. There were 186 such patients out of the entire population.

Radical resection of the lesion was performed 6 to 10 weeks after the completion of PCRT. All surgeries were performed according to the principle of TME. In cases of low rectal cancers, intersphincteric resection was performed if the circumferential and distal resection margins could be procured; if not, abdominoperineal resection was performed.

Pathologic examination was performed by pathologists specialized in colorectal cancer pathology. Staging was done according to the most updated AJCC Manual at the time of surgery. Pathologic responses to PCRT were evaluated in the resected specimens using the tumor regression grade (TRG) system according to the proportion of tumor cells as well as fibrosis, suggested by the Gastrointestinal Pathology Study Group of the Korean Society of Pathologists.[6] Those with near-total regression or total pathologic regression were defined as "good responders," whereas those with minimal or moderate regression defined as "poor responders."

Surveillance and Oncologic Outcomes

Patients were monitored postoperatively for recurrence every 3 to 6 months for the first 2 years, every 6 months for the following 3 years, and annually thereafter. Physical examination, laboratory studies including carcinoembryonic antigen level, and an abdominopelvic computed tomography (CT) scan were performed every 6 months. Colonoscopy was performed every 2 to 3 years. When multiple polyps or polyps larger than 1 cm were identified, a colonoscopy was performed annually. Local recurrence was defined as the presence of a suspicious lesion at the site of anastomosis or at the site of the primary resection upon postoperative colonoscopy or pelvic imaging (CT, MRI, and/or positron emission tomography [PET] scan). Distant metastasis was defined as the presence of a recurrence beyond the operative fields, including in distant organs, detected by CT or PET. These were diagnosed based on biopsy and serial changes upon imaging diagnosis. Recurrence-free survival (RFS) and overall survival (OS) were calculated from the day of surgery to the date of the first recurrence event.

Statistical Analysis

The clinicopathologic characteristics were analyzed using the χ^2 and independent-sample t tests as well as logistic regression. Among these, ypN status was analyzed for each ypT stage. The oncologic outcomes were examined by juxtaposing the RFS and OS of patients with ypT0-2 and ypT3-4N disease using the Kaplan-Meier method with log-rank tests. Multivariate analyses were performed using the Cox proportional hazards model, with a 95% confidence interval (CI), to assess the risk factors associated with RFS and OS. Statistical significance was defined as $P < .05$, and all analyses were performed using IBM SPSS Statistics for Window, version 21.0 (IBM Corp, Armonk, NY) and R (R Core

Team [2013], R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinicopathologic Characteristics

The study included 728 and 675 patients with ypT0-2 and ypT3-4 disease, respectively. Compared with that in patients with ypT0-2 disease, a larger percentage of patients with ypT3-4 disease had lymphovascular invasion (2.61% vs. 16.8%; $P < .001$), perineural invasion (2% vs. 25%; $P < .001$), and circumferential resection margin involvement (0.6% vs. 7%; $P < .001$) (Table 1).

Categorization of the patients into 4 groups according to ypT and N stages (ie, ypT0-2N0 vs. ypT0-2N+ vs. ypT3-4N0 vs. ypT3-4N+) revealed no differences in the proportions of patients in each group who received sphincter-saving resection (79.3%, 71.4%, 76.6%, and 76.9%, respectively; $P = .352$) or adjuvant chemotherapy (85.4%, 89.3%, 89.6%, and 88.6%, respectively; $P = .087$) (Table 1).

Between patients with ypT0-2N+ and ypT3-4N0 disease, there was no difference in the proportion of patients who received adjuvant chemotherapy ($P = .89$) or sphincter preservation surgery ($P = .33$). In terms of cT category, cT2 disease was more common in ypT0-2N+ (10.7%) than in ypT3-4N0 (3.1%) disease ($P < .001$). cT3 diseases were the most common both in patients with ypT0-2N+ (84.5%) and ypT3-4N0 (80.5%) disease. cT4 disease was more common in patients with ypT3-4N0 (16.4%) than in ypT0-2N+ (4.8%) disease. There was no difference in initial clinical N+ status between patients with ypT0-2N+ (88.1%) and ypT3-4N0 (90.4%) disease ($P = .526$). Downstaging after PCRT was achieved in 92.9% of patients with ypT0-2N+ disease and 84.9% of patients with ypT3-4N0 disease ($P = .055$).

LN Metastasis According to ypT Category

Among patients with ypT3-4 disease, 42.9% (n = 290) had metastatic LNs. Analysis of patients with LN metastasis according to yp stage revealed a larger proportion of each population with LN metastasis and a higher average number of remnant metastasized LNs (1.6 ± 1.1 nodes in ypT0-2 and 3.2 ± 3.2 nodes in ypT3-4) with increasing ypT stage (Tables 1 and 2). Among patients with ypT0-2 disease, the proportion of those without LN metastasis was largest among patients with ypT0 disease, followed by those with ypT1 and ypT2 disease. Remaining metastatic LN(s) were observed in 11.5% (n = 84) of patients with ypT0-2 disease. With the exception of patients with ypT4 disease, who had an equal number of patients with 1 or 2 metastasized LNs, the largest proportion of patients of all ypT stages with LN metastasis had only 1 metastasized LN.

Oncologic Outcomes and Risk Factors in Patients With All Stages of Disease

The mean follow-up duration was 93.5 months. Patients with ypT0-2N+ and ypT3-4N0 disease showed different patterns of recurrence. Twenty-five percent of patients with ypT0-2N+ disease recurred in the form of distant metastasis, whereas 11.9% showed local recurrence. Among patients with ypT3-4N0 disease, 25.7% showed distant metastasis, whereas 4.9% had local recurrence. Both

Table 1 Clinicopathologic Characteristics

	ypT0-2N0 (N = 644), n (%)	ypT0-2N+ (N = 84), n (%)	ypT3-4N0 (N = 385), n (%)	ypT3-4N+ (N = 290), n (%)	*P*
Gender					.002
Female	227 (35.2)	35 (41.7)	99 (25.7)	107 (36.9)	
Male	417 (64.8)	49 (58.3)	286 (74.3)	183 (63.1)	
Mean age ± SD, y	58.9 ± 10.2	56.5 ± 10.7	58.6 ± 10.7	56.3 ± 10.6	.005
Examined LNs	14.5 ± 6.7	15.9 ± 6.3	16.7 ± 7.7	17.1 ± 7.4	<.001
Metastatic LNs	–	1.6 ± 1.1	–	3.2 ± 3.2	<.001
Lymphovascular invasion					<.001
Negative	603 (93.6)	78 (92.9)	348 (90.4)	213 (73.4)	
Positive	13 (2.0)	6 (7.1)	37 (9.6)	77 (26.6)	
Unchecked	28 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Perineural invasion					<.001
Negative	601 (93.3)	81 (96.4)	305 (79.2)	196 (67.6)	
Positive	14 (2.2)	3 (3.6)	79 (20.5)	93 (32.1)	
Unchecked	29 (4.5)	0 (0.0)	1 (0.3)	1 (0.3)	
Examined LNs	14.5 ± 6.7	15.9 ± 6.3	16.7 ± 7.7	17.1 ± 7.4	<.001
CRM					<.001
Negative	593 (92.2)	81 (96.4)	324 (84.2)	246 (85.1)	
Positive	4 (0.6)	1 (1.2)	27 (7.0)	21 (7.3)	
Unchecked	46 (7.2)	2 (2.4)	34 (8.8)	22 (7.6)	
SSR	511 (79.3)	60 (71.4)	295 (76.6)	223 (76.9)	.352
Adjuvant CTx	550 (85.4)	75 (89.3)	345 (89.6)	257 (88.6)	.087

Abbreviations: CRM = circumferential resection margin; CTx = chemotherapy; LN = lymph node; SSR = sphincter-saving resection.

Table 2 ypN Category According to ypT Category

pT	ypT0 (N = 276), n (%)	ypT1 (N = 86), n (%)	ypT2 (N = 366), n (%)	ypT3 (N = 639), n (%)	ypT4 (N = 36), n (%)
ypN					
0	257 (93.1)	77 (89.5)	310 (84.7)	367 (57.4)	18 (50.0)
1A	14 (5.1)	4 (4.7)	39 (10.7)	100 (15.6)	6 (16.7)
1B	4 (1.4)	3 (3.5)	15 (4.1)	88 (13.8)	6 (16.7)
2A	1 (0.4)	2 (2.3)	2 (0.5)	60 (9.4)	4 (11.1)
2B	0 (0.0)	0 (0.0)	0 (0.0)	24 (3.8)	2 (5.6)

local recurrence and distant recurrence occurred in 4.8% and 2.3% of patients with ypT0-2N+ and ypT3-4N0 disease, respectively Within those with recurrence, a higher percentage (37%) of patients with ypT0-2N+ disease showed local recurrence in comparison with patients with ypT3-4N0 disease (17.4%; $P = .024$), whereas 90.8% of patients with ypT3-4N0 disease and 77.8% of patients with ypT0-2N+ disease had distant metastasis. There was no statistical difference between the 2 groups in terms of distant metastasis ($P = .089$).

The 5-year RFS was 74.5% for all patients and was 88.9%, 66.7%, 71.1%, and 47.5% for patients with ypT0-2N0, T0-2N+, T3-4N0, and T3-4N+ disease, respectively ($P < .001$). The ypT0-2N+ group had a lower RFS rate compared with that of the ypT3-4N0 group, but the difference was not statistically significant ($P = .540$) (Figure 1).

Similar to the RFS, the 5-year OS differed significantly when patients were grouped according to ypT and ypN stages (Figure 2). The 5-year OS for all patients was 84.5% and was 93.5%, 78.6%, 82.9%, and 68.3%, respectively, for patients with ypT0-2N0, ypT0-2N+, ypT3-4N0, and ypT3-4N+ disease ($P < .001$). The patients with ypT3-4N0 disease survived longer than those with ypT0-2N+ disease, but the difference was not statistically significant ($P = .565$).

In multivariate analysis, LN metastasis, advanced ypT stage, perineural invasion, and sphincter-preserving resection were associated with RFS in all patients (Table 3). Among patients with ypT0-2 disease, those without metastatic LNs had a significantly longer RFS period than that in patients with metastatic LNs (Table 4). Among patients with ypT3-4 disease, those without metastatic LNs also had a longer RFS period (Table 3). Perineural invasion was significantly correlated with RFS (Table 4). A higher ypT stage was also correlated with an increased chance of recurrence (HR, 1.119), but the difference was not statistically significant ($P = .3438$)

Regarding OS, multivariate analysis revealed LN metastasis, ypT stage, patient age, perineural invasion, circumferential resection margin involvement, and sphincter preservation to be risk factors (Table 3).

Figure 1 Recurrence-free Survival According to ypT/N Stage. Recurrence-free Survival Was Stratified According to ypT/N Stage, With No Statistically Significant Difference Between ypT3-4N0 and ypT0-2N+

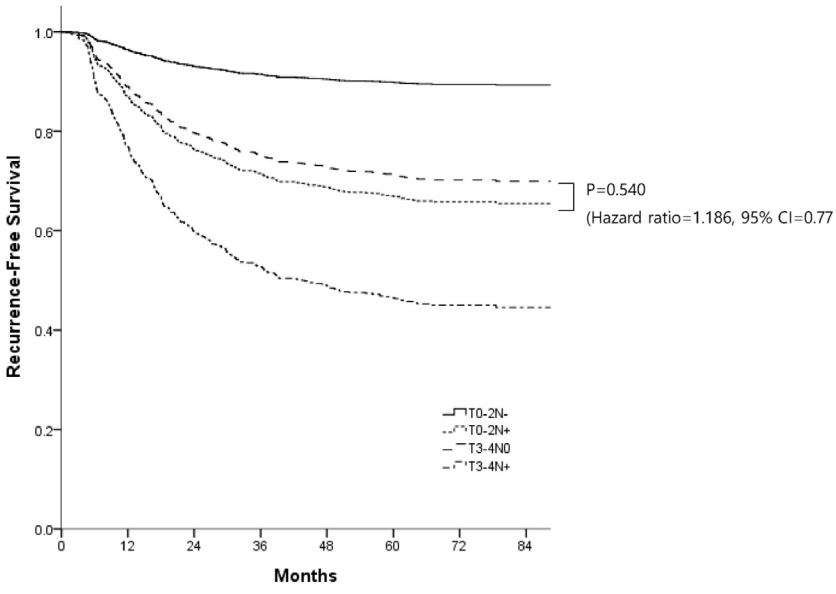
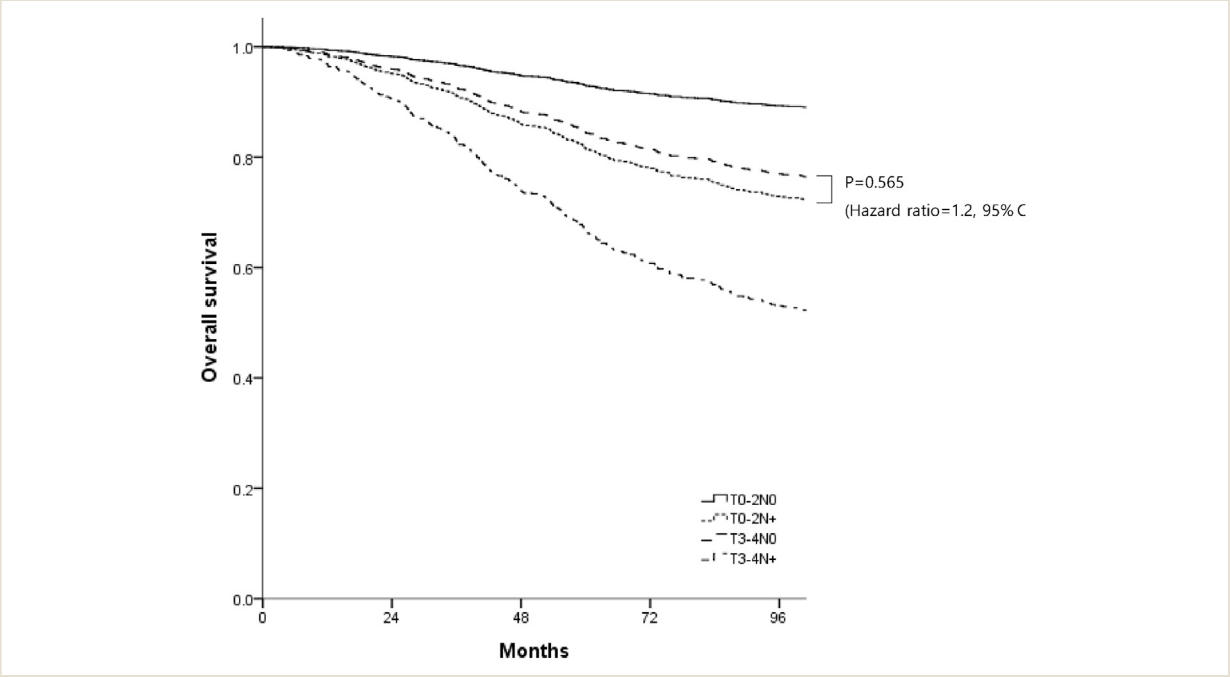


Figure 2 Overall Survival. Patients With ypT2-0N+ Disease Showed Unfavorable Overall Survival Compared With Patients With ypT3-4N0 Disease With No Statistical Significance



Oncologic Outcome of Patients According to TRG in Patients With ypT0-2 Disease

Among patients with ypT0-2 disease according to pathologic TRG (total and near-total vs. others), 63.1% belonged to the total or near-total regression groups (ie, the good responders to PCRT). The percentage of patients with remnant LNs was significantly lower among good responders in comparison with poor responders (9.98% vs. 15.11%). However, patients who had achieved

Table 3 Risk Factors Associated With Recurrence-free Survival and Overall Survival, Multivariate Analysis

	Recurrence-free Survival			Overall Survival		
	HR	95% CI	*P*	HR	95% CI	*P*
ypT stage			<.001			<.001
ypT0-2	1			1		
ypT3-4	2.201	1.680-2.884		1.932	1.474-2.531	
ypN stage			<.001			
ypN0	1			1		<.001
ypN+	2.304	1.827-2.906		2.599	2.047-3.300	
LVI	1.255	0.936-1.681	.152	1.224	0.901-1.662	.332
PNI	1.726	1.342-2.218	<.001	1.768	1.354-2.309	<.001
SSR	0.702	0.555-0.889	.003	0.710	0.556-0.908	.006
CRM involvement	1.359	0.896-2.061	.353	1.363	0.861-2.158	.180
Adjuvant CTx	0.929	0.437-1.975	.330	0.290	0.167-0.505	<.001
Gender			.476			.010
Male	1			1		
Female	1.087	0.865-1.366		1.382	1.082-1.765	
Age	0.999	0.999-1.009	.853	1.028	1.017-1.040	<.001

Abbreviations: CI = confidence interval; CRM = circumferential resection margin; CTx = chemotherapy; HR = hazard ratio; LVI = lymphovascular invasion; PNI = perineural invasion; SSR = sphincter-saving resection.

Table 4 Risk Factors Associated With Recurrence-free Survival in Patients With ypT0-2 and ypT3-4 Disease, Multivariate Analysis

	ypT0-2			ypT3-4		
	HR	95% CI	*P*	HR	95% CI	*P*
ypN stage			<.001			
ypN0	1			1		<.001
ypN+	3.290	2.058-5.261		2.073	1.601-2.684	
LVI	0.815	0.251-2.647	.942	1.357	1.006-1.830	.045
PNI	1.703	0.611-4.749	.309	1.774	1.369-2.299	<.001
SSR	0.676	0.429-1.066	.092	0.716	0.541-0.947	.019
Adjuvant CTx	0.854	0.261-2.791	.793	0.918	0.338-2.498	.868
Gender			.201			.172
Male	1			1		
Female	0.756	0.492-1.161		1.212	0.920-1.596	
Age	0.990	0.970-1.010	.310	1.001	0.989-1.013	.844

Abbreviations: CI = confidence interval; CTx = chemotherapy; HR = hazard ratio; LVI = lymphovascular invasion; PNI = perineural invasion; SSR = sphincter-saving resection.

significant regression after PCRT still did not have better DFS or OS ($P = .211$ and $P = .356$ respectively).

Looking at the N0 and N+ groups separately, better TRG grade failed to result in better DFS or OS in either the N0 or N+ group ($P = .617$ and $P = .594$ for ypT0-2N0; $P = .463$ and $P = .925$ for ypT0-2N+ groups, respectively).

Discussion

In our study of 728 patients with ypT0-2 disease and 675 patients with ypT3-4 disease with mid and low rectal cancer treated with PCRT followed by radical resection, ypT and ypN stages were independent risk factors for RFS, allowing the stratification of patients into ypT0-2N0, ypT0-2N+/ypT3-4N0, and ypT3-4N+ groups that consecutively showed worse RFS and OS. Patients with ypT3-4 and ypT0-2N+ disease did not show statistically significant differences in terms of RFS and OS, although patients with ypT3-4N0 disease had a marginally better oncologic outcome than those with ypT0-2N+ disease.

The TNM staging system is widely accepted for the evaluation of risk and determination of relevant treatment. The system reflects oncologic outcome well even in patients treated with PCRT[3,7] and can be used to decide treatment strategy and compare outcome of various experimental treatment options. Patients with stage IIIA rectal cancer not treated with PCRT reportedly have better survival outcomes compared with those in patients with stages IIB-C diseases, nearing that in patients with stage I disease in previous reports analyzing the SEER database.[1,2] The current AJCC staging system was criticized on this note for seemingly overestimating the influence of LN metastasis.

There is growing evidence that postoperative pathologic nodal status is a key prognostic factor for oncologic outcome in patients with rectal cancer treated with PCRT.[1-4] In an Italian study of 82 patients with locally advanced resectable extraperitoneal rectal cancer (LARC),[8] ypN status was the most significant prognostic factor among patients with ypT3-4 disease, whereas a study by a Korean group that included 382 patients with LARC[9] reported ypN status as the strongest prognostic factor in patients with ypT0 disease. However, the incongruity of the oncologic outcome of yp stages IIIA and II disease with the AJCC staging system has yet to be confirmed. Remnant LN metastasis after PCRT may be considered particularly "resistant" to PCRT, yet their oncologic influence remains unclear, especially in patients with primary tumors that responded well to PCRT.

Reports regarding the oncologic impact of metastatic LNs in patients with ypT0-2 disease after PCRT have shown inconsistent results. In a retrospective study of 406 patients with ypT0-2 disease, LN metastasis was observed in 16.3% of patients who underwent radical resection following PCRT. Categorization by ypT stage revealed LN metastasis in 9.1%, 17.1%, and 20.8% of patients with yp0, ypT1, and ypT2 disease, respectively. In the previous study, the 5-year OS or RFS did not differ according to LN metastasis in patients with ypT0-2 disease (OS, 87.5% vs. 85.2%; RFS, 83.6% vs. 79.6%; $P = .28$). Based on the similar RFS and OS between patients with ypT0-2N0 and ypT0-2N+ disease, the authors concluded that TME was effective in providing local control. However, another study from the Korean Radiation Oncology Group[2] reported an association between LN metastasis and poor prognosis even in patients with a pathologically completely regressed primary tumor. They collected data from 333 patients with ypT0 tumors after PCRT followed by curative radical resection between 1993 and 2007 and found that the ypN status was the most relevant independent prognostic factor for both disease-free survival (DFS) and OS. The 5-year DFS and OS were 88.5% and 94.8%, respectively, in patients with ypT0N0 disease, and 45.2% and 72.8%, respectively, in patients with ypT0N+ disease ($P < .001$).

In the present study, LN metastasis had a more potent influence on RFS in patients with ypT0-2 disease than on those with ypT3-4 disease. A key new finding in our study was the poorer prognosis shown in the presence of metastatic LNs in the mesorectum (88.9% vs. 66.7%; $P < .001$) in rectal cancer confined within the bowel wall. The poorer survival in the node-positive group with ypT0-2 disease in our study signals a subset of more aggressive tumors that are likely to recur or may have already metastasized to a degree

not yet detectable by current diagnostic tools at the time of clinical staging. Even in the subset of patients with ypT0-2 disease whose tumors had undergone significant degree of regression (total or near total), DFS and OS did not show improvement in comparison with those with moderate or less regression.

Understanding the influence of metastatic LNs on oncologic outcome in patients with a significantly regressed primary tumor is important, considering the increased interest in organ-preserving strategies or deferral of surgery for such patients. It is all the more so, as evaluation of metastatic LNs after PCRT is still not without limitations. Organ-preserving approaches such as local excision or watch-and-wait (W&W) for patients with good response to PCRT have the benefits of avoiding surgical complications and the emotional and practical difficulties of living with a stoma. These practices were first devised based on the observation that, among patients who received surgery without PCRT, the LN metastasis rate among patients with T0-2 disease was low, and that, even with LN metastasis, tumors confined within the bowel wall still resulted in a better prognosis than those in patients without LN metastasis but with a deeper invasion depth, implying that the prognostic effect of LN metastasis in patients who did not receive PCRT was not as significant in T0-2 as it is in T3-4 disease.

Organ-preserving approaches have gained popularity since the reports from several studies showing that a good response to PCRT was a predictor for good RFS and OS.[10,11] One such study was that by Habr-Gama et al,[12] in which the 5-year OS and DFS were considerably lower in patients with an incomplete response to CRT compared with those in patients who were observed for recurrence without surgery after complete clinical response to CRT (88% and 83%, respectively, in the resection group and both 100% in the observation group).[12] A Dutch group[13] performed a similar study but prospectively found that the DFS and OS did not differ significantly between the W&W patients and the patients who underwent surgery ($P = .770$ for DFS; $P = .228$ for OS).[13] More recently, the oncologic outcomes of organ-preserving strategies for subgroups of patients clinically diagnosed with a complete response to PCRT were reportedly comparable to those of radical resection.8,9 The most recent and largest-to-date study on W&W was a recent multicenter observational registry study with the International Watch & Wait Database.[8] In this study, data from 1009 patients who received neoadjuvant treatment and management by W&W at 47 different institutes were logged in a registry for prospective observation. Among them, 880 (87%) achieved a clinical complete regression (cCR) after CRT; in a median follow-up time of 3.3 years, the 2-year cumulative local regrowth rate was 25.2%; 97% of the associated tumors were located within the bowel wall, 87.8% of which could be salvaged by surgery.

The decision to adopt organ-preserving approaches in patients with a good response to CRT can be safe under 2 premises: the evaluation of post-PCRT tumor status is sufficiently accurate, and the cCR status has a high prognostic significance. The results of the 2 above-mentioned studies and several others corroborate the second premise of organ-preserving approaches: the reliable prognostic value of cCR status. Although we did not change treatment plans according to post-PCRT clinical stage, our analysis did not reveal a stratification of prognosis according to clinical staging (data not shown). In addition, in our study, one-fifth of patients with ypT0-2N+ disease who had achieved a cCR after PCRT had a poorer survival than those without metastatic LNs.

The current diagnostic method for clinical staging has its limits in both T and N staging.[14,15] Modified tools utilizing MRI such as mrTRG[16] (tumor regression grade on MRI images after PCRT) have been devised to improve clinical evaluation to better correspond to the pathologic evaluation. MrTRG and other MRI-measured parameters such as circumferential resection margin are associated with oncologic outcome,[5,17] as was in our data (Table 1); there remains a limitation in assessing the tumor response to PCRT.[18] Post-PCRT evaluation of response is particularly tricky regarding nodal status, as LNs become smaller and even disappear after PCRT.[19,20] Considering the limitation in current diagnostic methods in assessing post-PCRT clinical stage, we should also consider the oncologic outcomes after standard radical resection in deciding the following surgical strategies. Currently, many surrogate markers predicting oncologic outcome such as NAR (Neoadjuvant Rectal Score) and EMVI (extramural vascular invasion) are now being suggested. The NAR score was developed as a short-term clinical trial surrogate endpoint to take variables associated with treatment effect beyond ypCR into consideration. The NAR score is calculated based on data supported by the Valentini nomogram for OS, but only using the clinical T stage and pathologic T and N stages. Both continuous and categorical NAR were validated as effective predictive markers of 5-year OS.[21] Along with the association of histologic EMVI with poor oncologic outcomes,[22] MRI-detected EMVI has been known as an indicator of poorer oncologic outcomes.[23] Although not analyzed in the present study, these surrogate markers of oncologic outcome will be worthy of investigating in future studies to add knowledge on prognostication of PCRT-treated rectal cancer.

The results of the present study suggest that more attention needs to be paid to nodal status after PCRT. Better prognosis had been paradoxically observed in patients with pT0-2N+ disease despite being staged higher than patients with pT3N0 disease in the past.[1,2] In our study, ypN+ status predicted a worse prognosis even in tumors with good response to PCRT (ie, ypT0-2 tumors). The RFS and OS of patients with ypT0-2N+ disease deteriorated to the extent that they were comparable to those of patients with ypT4N0 disease (67.3% vs. 63%; $P = .361$). Viewing this finding in light of studies discussed above, we conclude that the decision to withhold patients from complete local control by TME needs to be made with caution: nodal positivity, not readily detectable with the tools used in clinical staging, could be more lethal than previously believed in patients with rectal cancer that have not undergone PCRT. For clinicians to safely defer radical resection, the evaluation of the regression of LARC after CRT requires improvements in both technique and criteria consensus.

This study adds value in the field of colorectal cancer in that we assessed the prognosis of a growing yet under-analyzed subset of patients with colorectal cancer (ie, post-PCRT patients with rectal cancer). The limitations of this study include its retrospective nature and that the patient data were collected metachronously from a single center. Also, given a small number of patients with ypT4a and ypT4b disease, we were unable to compare the specific groups to patients with ypT0-2N+ disease, and instead grouped them as a wider spectrum of patients (ie, ypT3-4N0). A prospective study

with a wider pool of patients throughout or beyond the nation with universal treatment guidelines could produce more comprehensive, less biased results.

Conclusion

The oncologic outcomes of ypT0-2N+ disease were not favorable compared with those of ypT3-4N0 disease in patients with rectal cancer treated with PCRT. These outcomes dispute the survival paradox traditionally believed for non-PCRT-treated patients with rectal cancer, and highlight the underestimated significance of post-PCRT nodal involvement.

Clinical Practice Points

- The prognostic importance of metastatic LNs should be carefully considered when deciding the surgical strategy after PCRT.
- There often is discordance between post-PCRT clinical staging and final pathologic staging after surgery, especially in nodal status.
- Considering the worse outcome shown in patients with ypT0-2 disease with remnant lymph nodes, a more scrupulous examination of tumor profile needs to be taken in deciding the post-PCRT treatment strategy for the patient.

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Disclosure

The authors have stated that they have no conflicts of interest.

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