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Pathologic Staging Inconsistency Between ypT4N0 (stage II) and ypT1-2N1 (stage III) After Preoperative Chemoradiotherapy and Total Mesorectal Excision in Rectal Cancer: A Multi-Institutional Study

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Abstract

Patients with rectal cancer patients with ypT4N0 (stage II) showed worse recurrence-free survival than those with ypT1-2N1 (stage III). Patients staging ypT4N0 (stage II) had significantly higher locoregional recurrence and distant metastasis rates than those staging ypT1-2N1 (stage III). ypT4N0 (stages II) should be classified to a higher stage in the rectal cancer staging system.

Background: In the Surveillance, Epidemiology, and End Results population-based data, the survival curves reversed between T4N0 (stages IIB or IIC) and T1-2N1 (stage IIIA) in rectal cancer. However, T4N0 had a higher stage than T1-2N1 in the current colorectal staging system. **Patients and Methods:** We analyzed 1804 patients with rectal cancer who were treated with preoperative chemoradiotherapy and curative surgery. We grouped patients by pathologic stage, and recurrence-free survival (RFS) and overall survival rates were calculated and compared for each stage. We evaluated prognostic factors that influenced recurrence and survival. **Results:** In the recurrence and survival analysis, 3-year RFS rates were 95.9% for ypStage 0, 94.0% for ypStage I, 78.9% for ypStage IIA, 55.8% for ypStage IIB/C, 80.2% for ypStage IIIA, 64.6% for ypStage IIIB, and 44.9% for ypStage IIIC. Patients with ypStage IIB/C showed significantly worse RFS ($P = .004$) than did those with ypStage IIIA. The ypStage IIB/C group showed significantly higher rates of both locoregional recurrence (24.3% vs. 5.5%; $P = .02$) and distant metastasis (31.6% vs. 17.1%; $P = .048$) than did the ypStage IIIA group. Compared with ypStage IIIA, ypStage IIB/C showed significantly higher pre-chemoradiotherapy carcinoembryonic antigen ($P = .004$), circumferential radial margin involvement ($P = .001$), and positive perineural invasion ($P = .014$). **Conclusion:** Patients with rectal cancer staged ypT4N0 were associated with higher locoregional recurrence and distant metastasis rates than those staged ypT1-2N1 in the current staging system.

Clinical Colorectal Cancer, Vol. 18, No. 1, e130-9
Keywords: Chemoradiation, Pathologic stage, Prognosis, Rectal cancer, Survival

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Submitted: Sep 17, 2018; Revised: Nov 12, 2018; Accepted: Nov 16, 2018; Epub: Nov 23, 2018

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1533-0028/$ - see frontmatter
https://doi.org/10.1016/j.clcc.2018.11.003

Introduction

The tumor, lymph node, and metastasis (TMN) staging system of the American Joint Committee on Cancer (AJCC) is widely adopted to predict outcomes and guide adequate treatments for patients with colorectal cancer.[1] The current TNM staging of colorectal cancer is based on the survival analysis of Surveillance, Epidemiology, and End Results (SEER) population-based data. From the SEER analysis results, rectal cancer is also classified as stages I to IV.[2]

In the seventh edition of the AJCC staging manual, there were some modifications of staging; stage T4 was weighted, and N2 stage was unweighted.[1] Stage II was subdivided into IIA (T3N0), IIB (T4aN0), and IIC (T4bN0), and stage III was subdivided into IIIA (T1-2N1 or T1N2a), IIIB (T3-4aN1, T2-3N2a or T1-2N2b), and IIIC (T4aN2a, T3-4aN2b or T4bN1-1). According to the previous SEER analysis, stages IIB or IIC (T4N0) did not show better survival outcomes than did stage IIIA (T1-2N1-2) in rectal cancer. Several other studies suggested that T stage was underestimated compared with N stage in colorectal cancer.[3-8] Despite this debate, the current AJCC staging system did not adjust the rectal cancer staging in the latest edition, the eighth.[9]

Colorectal cancer treatment is determined by clinical stage before oncologic care, and the standard of care for locally advanced colon cancer is curative surgery followed by adjuvant chemotherapy. However, preoperative chemoradiotherapy (CRT) and curative surgery are the optimal treatments in patients with locally advanced rectal cancer.[10-14] The exact pathologic confirmation of the initial clinical stage is impossible because of the pre-CRT phase in rectal cancer, and the pathologic evaluation after CRT is the most certain staging for physicians to predict the patient's prognosis in rectal cancer.

The purpose of this multi-institutional study was to clarify the argument for relevant staging of T4N0 (current stage IIB or IIC) and T1-2N1 (current state IIIA) rectal cancer. We analyzed oncologic outcomes for each stage and evaluated prognostic factors affecting recurrence and survival in patients with rectal cancer who received preoperative CRT and curative surgery.

Materials and Methods

Patients

This Korean Radiation Oncology Group study is a multi-center and retrospective analysis in which patients with advanced rectal cancer who received preoperative CRT and total mesorectal excision (TME) were enrolled.[15] The inclusion criteria for the study were patients with histologically confirmed rectal adenocarcinoma, distal margin of the tumor located within 10 cm of the anal verge, stage T3 or T4 confirmed clinically by magnetic resonance imaging, no evidence of distant metastasis, and no history of malignance except non-melanoma skin cancer. Each center obtained approval from its institutional review board and the Korean Radiation Oncology Group before patients were enrolled.

Treatment

Included patients received preoperative CRT to the pelvis at a dose of 45 Gy in 25 fractions, followed by boost to the primary tumor at a dose of 5.4 Gy in 3 fractions over 5.5 weeks. 5-fluorouracil (5-FU) chemotherapy was administered as concurrent therapy, either 2 cycles of bolus 5-FU (400 mg/m^2/day) and leucovorin (20 mg/m^2/day), continuous infusion of 5-FU (225 mg/m^2/day) during CRT or capecitabine (825 mg/m^2) twice daily. All patients received total mesorectal excision 4 to 8 weeks after the completion of CRT. Adjuvant chemotherapy with 5-FU or capecitabine was administered according to the institutional treatment policy.

Evaluation

All patients received clinical and pathologic staging workups. Before the preoperative CRT, initial diagnostic and staging workup consisted of digital rectal examination, endoscopy, chest and abdominopelvic computed tomography, pelvic magnetic resonance imaging, blood test including carcinoembryonic antigen, and/or endorectal ultrasonography. After surgical resection, pathologic evaluation was performed by experienced pathologists. The pathologic examination consisted of histologic grade, presence of lymph node metastasis, lymphovascular invasion (LVI), perineural tumour invasion (PNI), and circumferential radial margin (CRM). CRM was defined as an involvement when surgical clearance had been within 1 mm. We determined clinical and pathologic staging (ypStage) after CRT according to the TNM classification suggested by the seventh edition of the AJCC staging manual.

Statistical Analyses

Recurrence-free survival (RFS) was the time from surgery to the first event of either recurrence of rectal cancer, the last day of follow-up, or death. Overall survival (OS) was defined as the time from surgery to death from any cause or last follow-up date. Recurrence was defined as radiologic and/or pathologic evidence of locoregional recurrence or distant metastasis.

We plotted the survival curve using the Kaplan-Meier method, and we used the log-rank test to compare the survival between the groups. We used the Cox proportional hazards model to estimate the hazard ratios of the prognostic factors in the multivariate analysis. We considered $P < .05$ as statistically significant. We analyzed all data using R version 3.4.0 (R Foundation for Statistical Computing).

Results

The study group consisted of 1804 patients with rectal cancer who were enrolled from 8 tertiary institutions (first institution, 597 patients; second institution, 308; third institution, 275; fourth institution, 271; fifth institution, 170; sixth institution, 127; seventh institution, 48; and eighth institution, 8). The patients were diagnosed with primary rectal cancer and received preoperative CRT followed by curative surgery. Clinicopathologic patient characteristics are shown in Table 1. We included 1238 (68.6%) males and 566 (31.4%) females, and the mean age was 61 years for all patients. The median pre-CRT carcinoembryonic antigen (CEA) was 3.4 ng/mL, and 1181 patients (65.5%) had CEA of $>$ 5 ng/mL. The median number of harvested lymph nodes was 14 (range, 10-21), and 57 (3.2%) patients showed positive radial margins after curative surgery. The median interval from completion of preoperative CRT to surgical resection was 7.2 weeks. Most patients, 1532 (84.9%) of 1804, received adjuvant chemotherapy. In the staging after preoperative CRT, 188

Table 1 Patient Characteristics

	ypStage 0-I (n = 667), n (%)	ypStage II (n = 579), n (%)	ypStage III (n = 558), n (%)	Total (n = 1804), n (%)	*P*
Age, y					.660
< 65	387 (58.0)	343 (59.2)	348 (62.4)	1078 (59.8)	
≥ 65	280 (52.0)	236 (40.8)	210 (37.6)	726 (40.2)	
Gender					.204
Female	227 (34.0)	167 (29.0)	172 (31.0)	566 (31.4)	
Male	440 (66.0)	412 (71.3)	386 (69.1)	1238 (68.6)	
CEA, ng/mL					< .001
≤ 5	514 (77.1)	333 (58.0)	334 (60.0)	1181 (65.5)	
> 5	153 (23.0)	246 (42.4)	224 (40.1)	623 (34.5)	
Differentiation					< .001
Well	144 (22.0)	87 (15.0)	55 (10.0)	286 (15.9)	
Moderate	503 (75.4)	456 (79.0)	446 (80.0)	1405 (77.9)	
Poor	20 (3.0)	36 (6.2)	57 (10.2)	113 (6.3)	
CRM					< .001
Negative	655 (98.2)	541 (93.4)	512 (92.0)	1708 (94.7)	
Positive	12 (2.0)	38 (7.0)	46 (8.2)	96 (5.3)	
LVI					< .001
Negative	531 (80.0)	456 (79.0)	319 (57.1)	1406 (77.9)	
Positive	36 (7.5)	123 (21.2)	239 (43.0)	398 (22.1)	
PNI					< .001
Negative	645 (97.0)	442 (76.3)	365 (65.4)	1452 (80.5)	
Positive	22 (3.2)	137 (24.0)	193 (35.0)	352 (19.5)	
Adjuvant chemotherapy					< .001
No	108 (16.1)	82 (14.1)	82 (15.0)	272 (15.1)	
Yes	559 (84.0)	497 (84.1)	476 (85.3)	1532 (84.9)	

Abbreviations: CEA = carcinoembryonic antigen; CRM = circumferential resection margin; LVI = lymphovascular invasion; PNI = perineural invasion.

(10.4%) patients achieved complete pathologic response (ypStage 0), 479 showed ypStage I, 579 showed ypStage II, and 558 showed ypStage III.

Recurrence and Survival

After a median follow-up time of 45.0 months (interquartile range, 26.3-66.5 months), we analyzed RFS and OS according to the pathologic stage (Table 2). The 3-year RFS rates were 95.9% for ypStage 0, 94% for ypStage I, 78.9% for ypStage IIA, 55.8% for ypStage IIB/IIC, 80.2% for ypStage IIIA, 64.6% for ypStage IIIB, and 44.9% for ypStage IIIC. In the log-rank test, the ypStage IIB/IIC group showed significantly worse RFS than the ypStage IIIA group ($P = .004$), and there was no significant difference in RFS between the ypStage IIIB ($P = .127$) and IIIC ($P = .546$) groups. ypStage IIIA showed similar results for RFS to those for ypStage IIA ($P = .929$) (Figure 1A).

Table 2 Summary of 3-year Oncologic Outcomes for Each Stage

ypStage	RFS Rate, %	OS Rate, %	Recurrence Rate, %	
			Locoregional	Distant
0	95.9	98.1	0	4.1
I	94.0	96.2	0.9	5.4
IIA	78.9	92.6	5.7	18
IIB/IIC	55.8	77.9	24.3	31.6
IIIA	80.2	90.4	5.5	17.1
IIIB	64.6	84.1	9.4	30.4
IIIC	44.9	65.1	11.7	53
All	80.4	91.2	4.7	16.9

Abbreviations: OS = overall survival; RFS = recurrence-free survival.

Figure 1 A, Kaplan-Meier Curves of Recurrence-free Survival for all Pathologic Stages in Rectal Cancer. B, Kaplan-Meier Curves of Overall Survival for All Pathologic Stages in Rectal Cancer. C, Locoregional Recurrence Rate for All Pathologic Stages in Rectal Cancer. D, Distant Metastasis Rate for All Pathologic Stages in Rectal Cancer

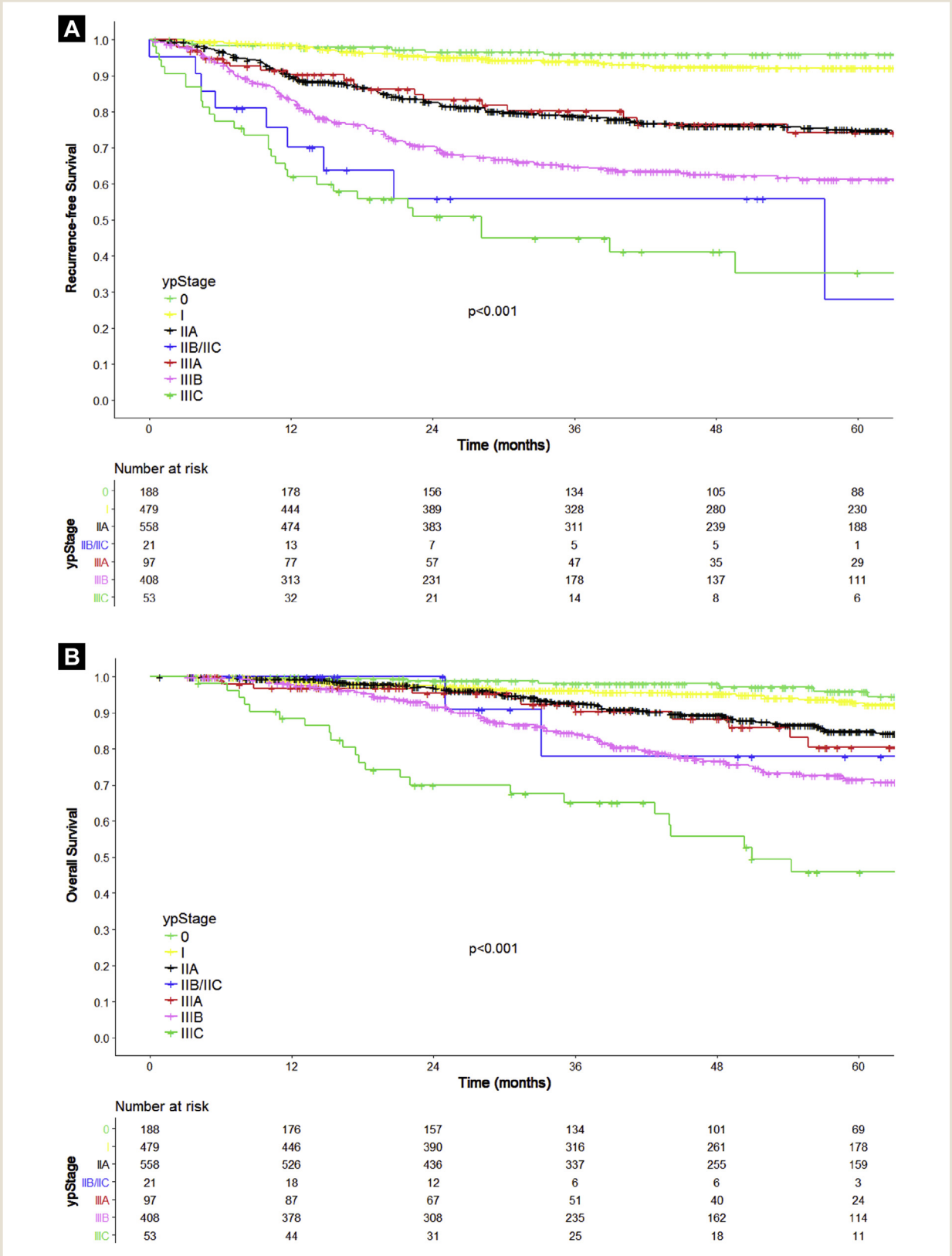

Figure 1 continued

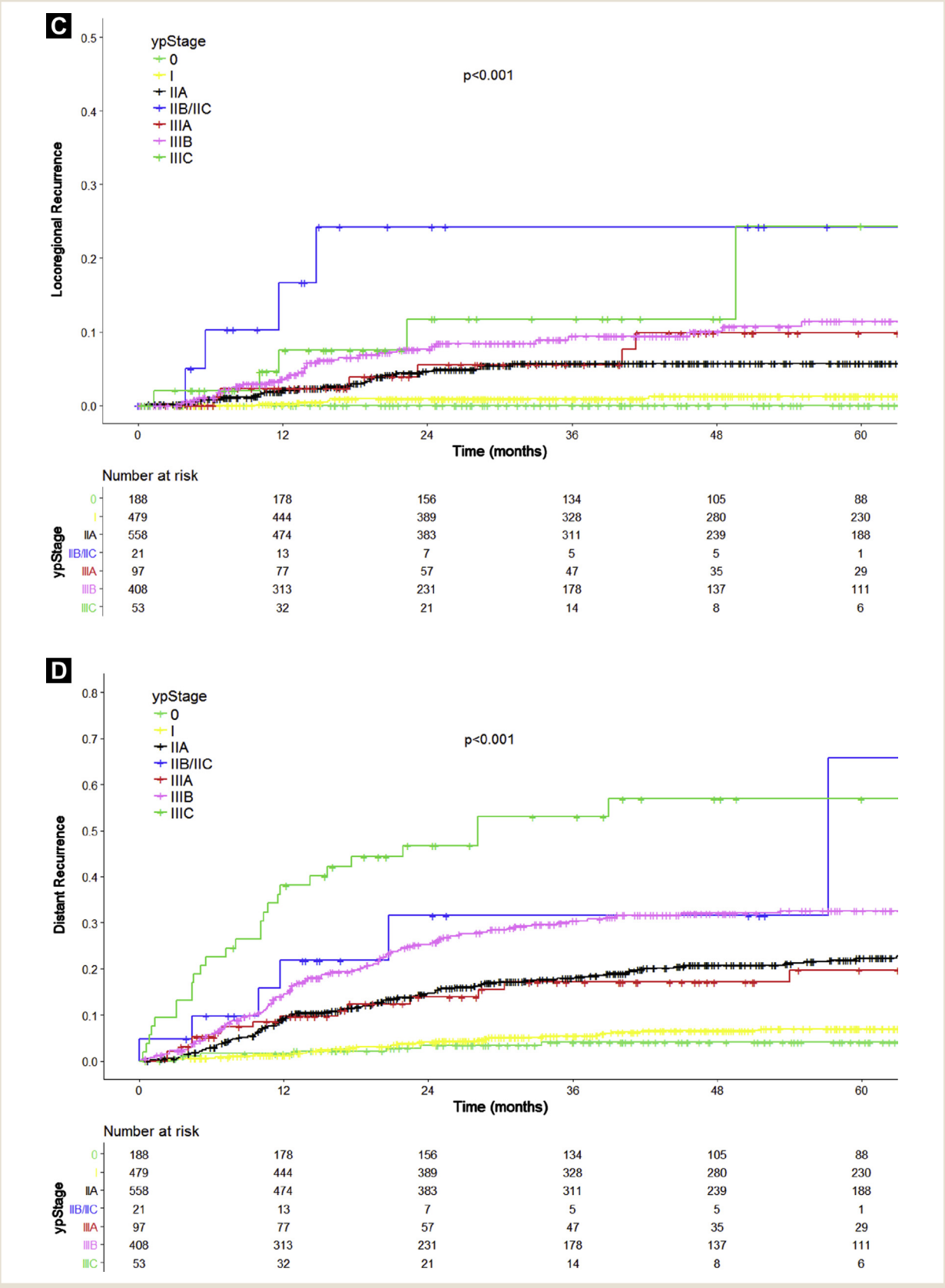

Table 3 Univariate and Multivariate Analyses of Prognostic Factors for Recurrence-free Survival

	N (%)	3-Year Rate, %	Univariate Analysis	Multivariate Analysis		
			P Value	Adjusted HR	95% CI	*P* Value
Age, y			.422			
< 65	1078 (59.8)	79.9				
≥ 65	726 (40.2)	81.3				
Gender			.454			
Female	566 (31.4)	78.5				
Male	1238 (68.6)	81.3				
CEA, ng/mL			< .001			.224
≤ 5	1181 (65.5)	82.8		Referent		
> 5	623 (34.5)	75.9		1.141	0.923-1.411	
ypStage			< .001			< .001
0	188 (10.4)	95.9		Referent		
I	479 (26.6)	94.0		1.614	0.747-3.489	
IIA	558 (30.9)	78.9		4.699	2.284-9.665	
IIB/IIC	21 (1.2)	55.8		7.522	4.769-32.881	
IIIA	97 (5.4)	80.2		5.662	2.489-12.884	
IIIB	408 (22.6)	64.6		7.603	3.673-15.735	
IIIC	53 (2.9)	44.9		11.801	5.135-27.119	
Differentiation			< .001			.498
Well to moderate	1691 (93.7)	81.4		Referent		
Poor	113 (6.3)	65.0		1.133	0.789-1.628	
CRM			<.001			.050
Negative	1708 (94.7)	81.7		Referent		
Positive	96 (5.3)	56.1		1.435	1.000-2.059	
LVI			< .001			.694
Negative	1406 (77.9)	83.3		Referent		
Positive	398 (22.1)	69.6		1.05	0.824-1.339	
PNI			< .001			< .001
Negative	1452 (80.5)	86.1		Referent		
Positive	352 (19.5)	56.4		1.993	1.566-2.536	
No. dissected lymph nodes			.187			.288
≥ 12	1206 (66.9)	82.6		Referent		
< 12	598 (33.1)	79.3		0.884	0.705-1.109	
Adjuvant chemotherapy			.987			
No	272 (15.1)	80.4				
Yes	1532 (84.9)	80.4				

Abbreviations: CEA = carcinoembryonic antigen; CI = confidence interval; CRM = circumferential resection margin; HR = hazard ratio; LVI = lymphovascular invasion; PNI = perineural invasion.

The 3-year OS rates for each ypStage were 98.1% for 0, 96.2% for I, 92.6% for IIA, 77.9% for IIB/C, 90.4% for IIIA, 84.1% for IIIB, and 65.1% for IIIC. In the log-rank test, ypStage I showed a similar result to that for ypStage 0 ($P > .05$), and ypStages IIA, IIB/C, and IIIA showed no survival difference (IIA vs. IIB/C, $P = .565$; IIB/C vs. IIIA, $P = .827$; and IIA vs. IIIA, $P = .609$). ypStage IIIB showed significantly worse survival than that for ypStage IIA ($P < .001$) but not than those for ypStages IIB/IIC ($P = .602$) and IIIA ($P = .080$). ypStage IIIC showed the worst survival rate among the groups (Figure 1B).

The 3-year locoregional recurrence rates were 0% for ypStage 0, 0.9% for ypStage I, 3.9% for ypStage IIA, 24.3% for ypStage IIB/IIC, 5.5% for ypStage IIIA, 9.4% for ypStage IIIB, and 11.7% for ypStage IIIC. The 3-year distant metastasis rates were 4.1% for ypStage 0, 5.4% for ypStage I, 18.0% for ypStage IIA, 31.6% for ypStage IIB/IIC, 17.1% for ypStage IIIA, 30.4% for ypStage IIIB, and 53% for ypStage IIIC. In the log-rank test, the ypStage IIB/C group showed significantly higher rates of both locoregional recurrence (24.3% vs. 5.5%; $P = .02$) (Figure 1C) and distant metastasis (31.6% vs. 17.1%; $P = .048$) (Figure 1D) than did the ypStage IIIA group.

Table 4 Univariate and Multivariate Analyses of Prognostic Factors for Overall Survival

			Univariate	Multivariate		
	N (%)	3-Year Rate, %	*P* Value	Adjusted HR	95% CI	*P* Value
Age, y			< .001			< .001
< 65	1078 (59.8%)	92.8		Referent		
≥ 65	726 (40.2%)	88.5		1.744	1.347-2.258	
Gender			.173			.243
Female	566 (31.4%)	81.8		Referent		
Male	1238 (68.6%)	90.8		1.184	0.892-1.571	
CEA, ng/mL			< .001			.105
≤ 5	1181 (65.5%)	92.9		Referent		
> 5	623 (34.5%)	87.7		1.241	0.956-1.612	
ypStage			< .001			< .001
0	188 (10.4%)	98.1		Referent		
I	479 (26.6%)	96.2		1.494	0.686-3.253	
IIA	558 (30.9%)	92.6		2.162	1.026-4.557	
IIB/IIC	21 (1.2%)	77.9		3.256	1.428-9.881	
IIIA	97 (5.4%)	90.4		2.047	1.339-7.873	
IIIB	408 (22.6%)	84.1		3.763	1.778-7.966	
IIIC	53 (2.9%)	65.1		5.703	2.376-13.684	
Differentiation			< .001			.160
Well to moderate	1691 (93.7%)	91.7		Referent		
Poor	113 (6.3%)	83.1		1.351	0.888-2.056	
CRM			<.001			.005
Negative	1708 (94.7%)	92.1		Referent		
Positive	96 (5.3%)	73.4		1.875	1.209-2.906	
LVI			< .001			.015
Negative	1406 (77.9%)	92.9		Referent		
Positive	398 (22.1%)	84.6		1.453	1.077-1.961	
PNI			< .001			< .001
Negative	1452 (80.5%)	94.2		Referent		
Positive	352 (19.5%)	78.4		2.308	1.710-3.115	
No. dissected lymph nodes			.187			.908
≥ 12	1206 (66.9%)	90.8		Referent		
< 12	598 (33.1%)	91.4		1.017	0.766-1.350	
Adjuvant chemotherapy			.019			.100
No	272 (15.1%)	85.6		Referent		
Yes	1532 (84.9%)	92.1		0.505	0.339-1.753	

Abbreviations: CEA = carcinoembryonic antigen; CI = confidence interval; CRM = circumferential resection margin; HR = hazard ratio; LVI = lymphovascular invasion; PNI = perineural invasion.

Clinicopathologic Prognostic Factors

We analyzed the clinicopathologic factors for RFS (Table 3) and OS (Table 4). In the multivariate analysis, the pathologic stage was a significant prognostic factor for both RFS and OS (all $P < .001$). PNI was a significant prognostic factor for RFS (hazard ratio [HR], 1.993; 95% confidence interval [CI], 1.556-2.536; $P < .001$). There was an increased risk of RFS in the patients with positive CRM (HR, 1.435; 95% CI, 1.000-2.059; $P = .050$). Age (HR, 1.744; 95% CI, 1.347-2.258; $P < .001$), CRM (HR, 1.875; 95% CI, 1.209-2.906; $P = .005$), LVI (HR, 1.453; 95% CI, 1.077-1.961; $P = .015$), and PNI (HR, 2.308; 95% CI, 1.710-3.115; $P < .001$) were significant prognostic factors for OS.

Comparison of Risk Factors Between ypStage IIB/C and ypStage IIIA

The clinicopathologic factors were compared between ypStages IIB/C and IIIA (Table 5). The patient's age at diagnosis was not significantly different between the 2 groups ($P = .601$). In the ypStages IIB/C groups, the incidence of pre-CRT CEA > 5 ng/mL

Table 5 Comparison of Risk Factors in ypStage IIB/C and ypStage IIIA Patients

	IIB/IIC (n = 21), n (%)	IIIA (n = 97), n (%)	Total (n = 118), n (%)	*P* Value
Age, y				
< 65	12 (57.1)	56 (57.7)	68 (57.6)	
≥ 65	9 (42.9)	41 (42.3)	50 (42.4)	
CEA, ng/mL				.004
> 5	11 (52.4)	19 (19.6)	30 (25.4)	
≤ 5	10 (47.6)	78 (80.4)	88 (74.6)	
CRM				.001
Negative	16 (76.2)	95 (97.9)	111 (94.1)	
Positive	5 (23.8)	2 (2.1)	7 (5.9)	
LVI				.115
Negative	20 (95.2)	75 (77.3)	95 (80.5)	
Positive	1 (4.8)	22 (22.7)	23 (19.5)	
PNI				.014
Negative	15 (71.4)	90 (92.8)	105 (89.0)	
Positive	6 (28.6)	7 (7.2)	13 (11.0)	
Adjuvant chemotherapy				.154
No	8 (38.1)	20 (20.6)	28 (23.7)	
Yes	13 (61.9)	77 (79.4)	90 (76.3)	

Abbreviations: CEA = carcinoembryonic antigen; CRM = circumferential resection margin; LVI = lymphovascular invasion; PNI = perineural invasion.

was significantly more frequent than it was in the ypStage IIIA group (52.4% vs. 19.6%; $P = .004$). Adjuvant chemotherapy was administered in 61.9% of patients with ypStages IIB/IIC and in 79.4% of patients with ypStage IIIA, and the difference was not significant between the 2 groups ($P > .05$). The incidences of positive CRM (23.8% vs. 2.1%; $P = .001$) and PNI (28.6% vs. 7.2%; $P = .014$) were significantly higher in the ypStages IIB/C groups than in the ypStage IIIA group.

Discussion

The depth of local tumor invasion and presence of lymph node metastasis are known to be risk factors for recurrence and survival in rectal cancer.[16] The TNM staging system adequately reflects these features, which is why it is widely accepted as a system for evaluating risk and determining the relevant treatment. The current, eighth edition of the TNM colorectal cancer staging system was based on the survival analysis results of pooled analyses and SEER population-based data.[2,17,18] In these series, Gunderson et al reported that OS for T4N0 patients was worse than that for T1-2N1 patients and even similar to that for T1-2N2 patients. The 5-year OS rate for T4N0 patients ranged from 50.4% to 65% and that for T1-2N1 patients ranged from 72.1% to 81%. However, the authors proposed T4N0 as stages IIB and IIC and T1-2N1 as stage IIIA.

Several studies highlighted this inconsistency. Kim et al reported oncologic outcomes for 359 patients with T4N0 or T1-2N1 colon cancer.[4] They reported that T4N0 colon cancer showed worse oncologic outcomes than did T1-2N1 colon cancer regardless of adjuvant chemotherapy (5-year OS rate; 84.0% vs. 92.3%; $P = .012$). Li et al analyzed the survival of 999 patients with rectal cancer.[6,7] In this study, 5-year OS rates were 55.7% for T4aN0, 44.7% for T4bN0, and 68.9% to 75.9% for T1-2N1. They concluded that T4N0 should be classified as stage III and T1-2N1 as stages I or II. Huang et al analyzed the SEER database and reported that 5-year cancer-specific survival rates for patients with rectal cancer stages IIB, IIC, and IIIA were 67%, 46%, and 80%, respectively. Compared with patients with stage IIIA rectal cancer, patients with stage IIB (HR, 1.493; 95% CI, 1.267-1.758; $P < .001$) and stage IIC (HR, 2.712; 95% CI, 2.319-3.171; $P < .001$) cancer showed worse cancer-specific survival.[3] Mori et al reported single-center survival data in patients with colon and rectal

Table 6 Published Studies Comparing Survival of Stage IIB/C With Stage IIIA Patients With Colorectal Cancer

Study	Diagnosis	Stage/TNM Category	No.	5-Year OS, %	5-Year DFS, %	Remark
Gunderson et al	Rectal cancer	T4N0	1587	50.5		SEER database
		T4aN0	818	55.7		
		T4bN0	769	44.7		
		T1-2N1	2008	72.1		
Mori T et al	Rectal cancer	IIB	81	77.6		
		IIC	9	66.7		
		IIIA	48	87.3		
Huang et al	Rectal cancer	IIB	693	67[a]		SEER database
		IIC	587	46[a]		
		IIIA	1904	80[a]		
Li et al	Colorectal cancer	II	819	75.3		
		IIIA	74	86.2		
Kim et al	Colon cancer	T4N0	224	84	73.6	
		T1-2N1	135	92.3	88	

Abbreviations: DFS = disease-free survival; OS = overall survival; SEER = Surveillance, Epidemiology, and End Results program.
[a]Cancer-specific survival.

cancer. The 5-year OS rates were 77.6% for stage IIB, 68.7% for stage IIC, 87.3% for stage IIIA, and 69.2% for stage IIIB.[8] These results are summarized in Table 6.

We analyzed oncologic outcomes in patients with locally advanced rectal cancer using pathologic stage. Once again, preoperative CRT followed by TME was the treatment of choice for resectable stages II and III rectal cancer. This means that histologic confirmation of an initial disease is difficult, and what we can see is real pathologic stage after CRT. Furthermore, good response to CRT is a favorable predictor of local control and survival.[19] As a result, pathologic stage is a more accurate predictor of prognosis in patients with rectal cancer who received preoperative CRT followed by TME than pre-CRT clinical stage. For this reason, we performed survival analyses in the patients with advanced rectal cancer by pathologic stage. In our study, patients with ypStages IIB/C showed significantly worse RFS (55.8% vs. 80.2%; $P = .004$) than did ypStage IIIA. Both locoregional recurrence (24.3% vs. 5.5%; $P = .02$) and distant metastasis (31.6% vs. 17.1%; $P = .048$) were more common in the ypstage IIB/C group compared with the ypstage IIIA group. These were similar results with those of above-mentioned studies. Multivariate analyses revealed that positive CRM and perineural invasion were prognostic factors for both RFS and OS. ypStages IIB/C is a category of T4N0 in the current TNM staging system, which means that the tumor invades the visceral peritoneum or adheres to an adjunct organ or structure. In these cases, it is more difficult to achieve clear CRM than it is with less invasive tumors. Positive CRM is a significant risk factor for recurrence and survival and cannot be easily overcome by perioperative CRT.[20-23] In our multi-center study, positive CRM was significantly more frequent in ypStages IIB/C than in ypStage IIIA. PNI is still a well-known independent prognostic factor of both RFS and OS in colorectal cancer.[24] The incidence of PNI was also significantly higher in ypStages IIB/C than in ypstage IIIA in our analyses.

There were some limitations in our study. First, it was a multi-institutional retrospective analysis. Thus, there is a possible bias stemming from the diversity of radiation oncologists and surgeons.[25] However, we analyzed a large number of patients with advanced rectal cancer who received homogenous neoadjuvant therapy and surgical resection. Second, we analyzed a somewhat small number of patients with ypStages IIB and IIC cancer; only 21 (1.2%) of all patients had ypStages IIB or IIC cancer, which showed weak statistical power. Few patients had stages IIB/C (T4N0) rectal tumors; from 1992 to 2004, 35,829 patients with rectal cancer were registered in the SEER database, and only 1587 (4.4%) patients were in stages IIB or IIC.[2] A Norwegian population study reported only 5.4% of patients with advanced rectal cancer were identified as ypT4 after preoperative CRT followed by TME from 2007 to 2011.[26] To our knowledge, this is the first study that compared ypStage IIB/IIC with ypStage IIIA rectal cancer. Many previously published studies that evaluated rectal cancer by stages did not subdivide stage II into stages IIA, IIB, and IIC, but the prognosis for stage IIA rectal cancer is different from those for stages IIB or IIC rectal cancer.[2] For this reason, we separated ypStage IIA from ypStages IIB and IIC.

Conclusion

In conclusion, patients with rectal cancer with ypStages IIB/C showed a worse prognosis than those with ypStage IIIA in the current staging system. According to our multi-institutional analyses, we suggest that T4N0 (stages IIB/C) should be classified to a higher stage and T1-2N1 (stage III) into lower stage in the next rectal staging system. A multi-national validation study for rectal cancer staging is also indicated in the future time.

Clinical Practice Points

- In previous several studies, T stage was underestimated compared with N stage in colorectal cancer staging. Despite this debate, the current AJCC staging system still did not adjust the rectal cancer staging in the latest edition, the eighth.
- In this multi-institutional study, we clarify the argument for relevant staging of T4N0 (current stage IIB or IIC) and T1-2N1 (current state IIIA) rectal cancer. We analyzed oncologic outcomes for each stage and evaluated prognostic factors affecting recurrence and survival in patients with rectal cancer who received preoperative CRT and curative surgery.
- Patients with rectal cancer with ypStages IIB/C showed significantly worse locoregional recurrence and distant metastasis rates than those with ypStage IIIA in the current staging system. According to our multi-institutional analyses, we suggest that T4N0 (stages IIB/C) should be classified to a higher stage and T1-2N1 (stage III) into a lower stage in the next rectal staging system. A multi-national validation study for rectal cancer staging is also indicated in the future.

Acknowledgments

The statistical analyses performed in this article were advised by Catholic Medical Center Clinical Research Coordinating Center.

Disclosure

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

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