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Orignal Article

Significance of perineural and lymphovascular invasion in locally advanced rectal cancer treated by preoperative chemoradiotherapy and radical surgery: Can perineural invasion be an indication of adjuvant chemotherapy?

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ABSTRACT

Purpose: To investigate the prognostic significance of lymphovascular space invasion (LVI) and perineural invasion (PNI) in rectal cancer.
Methods and materials: Clinical data of 1,232 stage II–III rectal cancer patients from six tertiary institutions were analyzed. All patients were treated by long-course preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME). Adjuvant systemic chemotherapy was performed for 962 (78.1%) patients according to the multidisciplinary team's decision. Treatment outcomes and prognostic factors were evaluated according to the lymphovascular invasion (LVI) and perineural invasion (PNI) status.
Results: Five-year overall survival (OS) and recurrence-free survival (RFS) rates of the entire cohort were 84.1% and 71.1%, respectively. There is a significant difference in 5-year OS among both-absent, LVI+ only, PNI+ only, and both-present groups (89.1% vs. 77.9% vs. 67.6% vs. 56.2%; $p < 0.001$). RFS at five years was significantly different among both-absent, LVI+ only, PNI+ only, and both-present groups (78.7% vs. 58.7% vs. 44.6% vs. 38.6%; $p < 0.001$). The 5-year distant failure-free survival (DFFS) rate was also significantly different among four groups (84.6% vs. 61.4% vs. 54.2% vs 48.6%; $p < 0.001$). Although adjuvant chemotherapy did not affect 5-year DFFS in the entire cohort, adjuvant chemotherapy significantly reduced the distant failure rate in patients with PNI+ patients (44.9% vs. 54.6%, $p = 0.048$), not LVI+ patients (65.0% vs. 56.1%, $p = 0.487$).
Conclusion: Compared to LVI, PNI is a more significant prognostic factor in stage II–III rectal patients treated by preoperative CRT and TME surgery. The status of PNI rather than LVI could be an indicator for identifying patients who could benefit from adjuvant systemic chemotherapy.

After the publication of German rectal cancer study, preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is regarded as the standard treatment of locally advanced rectal cancer [1–4]. With this multi-disciplinary treatment, the locoregional recurrence rate has dropped to almost below 10% [3,4]. However, the distant failure rate is still over 20–30%. Distant metastasis is a crucial factor that affects the rectal cancer patient's survival. To overcome distant failures, adjuvant systemic chemotherapy after preoperative CRT and curative surgery is recommended widely, although several studies have failed to establish the beneficial role of adjuvant systemic chemotherapy [5–9]. There is still no definite conclusion on which patients need adjuvant systemic chemotherapy or which regimen can be the most effective to them.

Along with tumor and nodal stage, carcinoembryonic antigen (CEA) level, tumor regression grade, and surgical margin status, and the presence of lymphovascular invasion (LVI) and perineural

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invasion (PNI) have been reported as prognostic factors for colorectal cancer [10–13]. To detect cancer cells in peritumoral vessels and neurons may be a sign of metastatic potentials of them. However, only a few studies have reported the prognostic significance of LVI and PNI with regard to adjuvant chemotherapy in rectal cancer patients treated by preoperative CRT and curative surgery [10,12].

Will patients with LVI or PNI have higher risk of distant failure? Will patients with LVI or PNI benefit from adjuvant systemic chemotherapy? This study was conducted to find answers for these questions.

Materials and methods

Patients

Clinical data of 1,232 rectal cancer patients treated from 2005 to 2014 at 6 tertiary institutions were retrospectively collected by the following criteria: (1) Clinical T3-4 or node-positive pathologically diagnosed rectal adenocarcinoma, (2) treated by preoperative CRT and TME surgery, (3) no evidence of distant metastasis, and (4) Karnofsky's performance status over 70.

Treatment characteristics

All patients received long-course preoperative CRT with a fraction dose of 1.8 Gy up to a total dose of 50.4 Gy. Concurrent chemotherapy regimens were as follows: (1) two cycles of bolus intravenous 5-FU (400 mg/m^2/day) and leucovorin (20 mg/m^2/day) given at the first and fifth weeks of radiotherapy; (2) oral administration of capecitabine (825 mg/m^2/day) twice daily; and (3) continuous infusion of 5-FU (225 mg/m^2/day) during radiotherapy. After the end of combined treatment, all patients received radical TME surgery 4–8 weeks after completion of preoperative CRT. Of 1232 patients, adjuvant systemic chemotherapy was performed in 962 (78.1%) patients according to the clinician's or multidisciplinary team's decision. Adjuvant chemotherapy regimens were 4 monthly cycles of intravenous 5-fluorouracil (425 mg/m^2/day) and leucovorin (40 mg/m^2/day) on five consecutive days in 900 (93.5%) patients or 6 cycles of FOLFOX regimen in 62 (6.5%) patients. FOLFOX consisted of a 2-hour infusion of oxaliplatin (85 mg/m2) and leucovorin (400 mg/m^2) followed by a bolus injection of 5-FU (400 mg/m^2) and a continuous infusion of 5-FU (total 2400 mg/m^2) for 46 h, repeated every 2 weeks.

Pathologic examination

Pathologic specimens were evaluated using the standardized protocol of the College of American Pathologists by specialized colorectal pathologists in each institution [14]. The tumor size, pathologic cell type, invasion depth, presence of lymph node metastasis, histologic grade, differentiation, resection margin, LVI, PNI, and tumor response to the neoadjuvant therapy were evaluated by the protocol. Low grade represents well or moderately differentiated histology and high grade represents poorly differentiated histology or mucinous carcinoma or signet ring cell cancer. Circumferential radial margin (CRM) was defined as an involvement when the tumor was within 1 mm or less of the margin. LVI was defined as the presence of tumor cells within lymphatic or vascular spaces; identification of endothelial cells lining the space. PNI was defined as the presence of viable tumor cells within any layer of the nerve sheath or tumor foci outside of the nerve with involvement of the nerve's circumference in the perineural space.

Statistical analysis

Overall survival (OS) was defined as the time interval from the day of surgery to the day of death from any cause. Recurrence was recorded only as first event, not all events, during the follow-up period. Recurrence-free survival (RFS) was defined as the time interval from the day of surgery to the day of any recurrence or death. Locoregional failure-free survival (LFFS) and distant failure-free survival (DFFS) were defined as the time interval from the day of surgery to the day of first locoregional recurrence (inside the pelvis) or death and the day of distant recurrence (outside the pelvis) or death, respectively. Survival rates were calculated using the Kaplan–Meier method. Prognostic factors and survival curves were compared using the log-rank test. Statistical analysis was considered significant at $p < 0.05$. All factors that were significant in the univariate analysis were entered into Cox model in the multivariate analysis and hazard ratio (HR) was calculated with Cox model. All statistical analyses were performed using SPSS version 12.0 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

The median age of the entire cohort was 62 years (range, 27–83 years). There were 840 (68.2%) male and 392 (31.8%) female patients. 1120 (90.9%) patients had cT3 and 112 (9.1%) had cT4 stage. The clinical N stage was positive in 931 (75.6%) of 1232 patients. The median location of tumor was 5 cm (range, 0–10 cm) from the anal verge. The median tumor size was 4 cm (range, 0.5–14.0 cm). The initial CEA level had a median value of 3.4 (range, 0.4–50.0). The concurrent chemotherapy regimen was intravenous 5-FU based regimen in 1104 (89.6%) patients and oral capecitabine in 128 (10.4%) patients. All patients completed the preoperative CRT schedule. Anal sphincter-saving procedures were successfully done in 1,117 (90.7%) patients. In the pathologic examination, downstaging (ypT0-2 N0) was acquired in 482 (39.1%) patients and pathologic complete response (ypT0N0) was acquired in 174 (14.1%) patients. The presence of LVI was found in 185 (15.0%) patients and the presence of PNI was found in 211 (17.1%) patients. Eighty (6.5%) patients had both LVI and PNI while 916 (74.3%) patients had neither LVI nor PNI. Clinical characteristics among the four groups according to LVI and PNI status are shown in Table 1. In pathologic characteristics, patients in both-absent group had significantly lower clinical and pathologic T and N stage, lower initial CEA level, higher downstaging rate, and lower CRM involvement, as compared to the others (Table 2).

Survival outcomes and prognostic factors

OS and RFS rates at five years for the entire cohort were 84.1% and 71.1%, respectively. Locoregional recurrences occurred in 91 (7.4%) patients and distant metastasis developed in 277 (22.5%) patients at five years. Prognostic factors affecting LFFS, DFFS, RFS, and OS are analyzed and shown in Table 3. In the multivariate analysis, pathologic T and N stage, CRM involvement, and PNI were significant prognostic factors for locoregional recurrences. Pathologic T and N stage, CRM involvement, LVI, and PNI were significant factors for distant metastases. PNI status was a prognostic factor for all LFFS (HR, 2.89; $p < 0.001$), DFFS (HR, 1.78; $p < 0.001$), RFS (HR, 1.94; $p < 0.001$), and OS (HR, 2.43; $p < 0.001$). LVI status was a prognostic factor only for DFFS (HR, 1.41; $p = 0.043$), not LFFS (HR, 0.85; $p = 0.584$), RFS (HR, 1.23; $p = 0.156$), and OS (HR, 1.30; $p = 0.212$).

Table 1
Clinical patient characteristics among 4 groups according to lymphovascular and perineural invasion status (n = 1232).

	All absent (n = 916)	LVI+ only (n = 105)	PNI+ only (n = 131)	All present (n = 80)	p-Value
Age, year					0.769
≥65	383 (41.8)	42 (40.0)	50 (38.2)	30 (62.5)	
<65	533 (58.2)	63 (60.0)	81 (61.8)	50 (37.5)	
Sex					0.386
Male	616 (672)	71 (67.6)	92 (70.2)	61 (76.2)	
Female	300 (32.8)	34 (32.4)	39 (29.8)	19 (23.8)	
Clinical T stage					<0.001
T3	852 (93.0)	90 (85.7)	112 (85.5)	66 (82.5)	
T4	64 (7.0)	15 (14.3)	19 (14.5)	14 (17.5)	
Clinical N stage					0.012
N0	245 (26.7)	18 (17.1)	26 (19.8)	12 (15.0)	
N1-2	671 (73.3)	87 (82.9)	105 (80.2)	68 (85.0)	
Location from anus					0.789
<5 cm	359 (39.2)	37 (35.2)	51 (38.9)	34 (42.5)	
≥5 cm	557 (60.8)	67 (64.8)	80 (61.1)	46 (57.5)	
Tumor size					0.499
<4 cm	369 (40.3)	40 (38.1)	48 (36.6)	26 (32.5)	
≥4 cm	547 (59.7)	65 (61.9)	83 (63.4)	54 (67.5)	
Initial CEA level					<0.001
<5 ng/mL	283 (30.9)	36 (34.3)	71 (54.2)	31 (38.8)	
≥5 ng/mL	633 (69.1)	69 (65.7)	60 (45.8)	49 (61.2)	
CRT regimen					0.187
5-FU	826 (90.2)	91 (86.7)	120 (91.6)	67 (83.8)	
Capecitabine	90 (9.8)	14 (13.3)	11 (8.4)	13 (16.2)	
Operation technique					<0.001
LAR	842 (91.9)	100 (95.2)	109 (83.2)	66 (82.5)	
APR	74 (8.1)	5 (4.8)	22 (16.8)	14 (17.5)	
Adjuvant chemotherapy					0.001
No	210 (22.9%)	23 (21.9%)	25 (19.1%)	12 (15.0%)	
LF	674 (73.6%)	73 (69.5%)	95 (72.5%)	58 (72.5%)	
FOLFOX	32 (3.5%)	9 (8.6%)	11 (8.4%)	10 (12.5%)	

Abbreviations: APR, abdominoperineal resection; CEA, carcinoembryonic antigen; CRT, chemoradiotherapy; FOLFOX, leucovorin, 5-Flurorouracil, and oxaliplatin; LAR, low anterior resection; LVI, lymphovascular invasion; LF, leucovorin and 5-FU; PNI, perineural invasion.

Table 2
Correlation between pathologic factor and lymphovascular and perineural invasion status.

	All absent (n = 916)	LVI+ only (n = 105)	PNI+ only (n = 131)	All present (n = 80)	p-Value
Pathologic T stage					<0.001
T0-2	504 (55.0)	25 (23.8)	14 (10.7)	7 (8.8)	
T3-4	412 (45.0)	80 (76.2)	117 (89.3)	73 (91.2)	
Pathologic N stage					<0.001
N0	739 (80.7)	40 (38.1)	72 (55.0)	27 (33.8)	
N1-2	177 (19.3)	65 (61.9)	59 (45.0)	53 (66.2)	
Downstaging (ypT0-2 N0)	453 (49.5)	15 (14.3)	10 (7.6)	4 (5.0)	<0.001
Histologic grade					0.657
Low grade	863 (94.2)	97 (92.4)	122 (93.1)	73 (91.2)	
High grade	53 (5.8)	8 (7.6)	9 (6.9)	7 (8.8)	
CRM involvement					<0.001
Negative	834 (91.0)	96 91.4)	84 (64.1)	62 (77.5)	
Positive	82 (9.0)	9 (8.6)	47 (35.9)	18 (22.5)	

Abbreviations: CRM, circumferential resection margin; LVI, lymphovascular invasion; PNI, perineural invasion.

Table 3
Multivariate analysis for locoregional failure-free survival, distant failure-free survival, recurrence-free survival, and overall survival.

Hazard ratio (95% CI and p-value)	LFFS	DFFS	RFS	OS
Pathologic T stage (ypT0-2 vs. T3-4)	**2.18 (1.03–4.59, 0.041)**	**2.49 (1.69–3.67, <0.001)**	**1.92 (1.41–2.60, <0.001)**	1.09 (0.71–1.69, 0.692)
Pathologic N stage (ypN0 vs. N+)	**2.12 (1.28–3.49, 0.003)**	**1.57 (1.18–2.10, 0.002)**	**1.66 (1.30–2.12, <0.001)**	**1.77 (1.23–2.54, 0.002)**
Tumor regression grade (Grade 3–4 vs. 0–2)	1.76 (0.98–3.19, 0.061)	1.18 (0.86–1.61, 0.309)	1.26 (0.97–1.64, 0.081)	**1.61 (1.07–2.42, 0.022)**
Histologic grade (Low vs. High)	1.47 (0.67–3.22, 0.341)	1.22 (0.77–1.92, 0.398)	1.46 (1.00–2.12, 0.050)	1.72 (1.00–2.96, 0.052)
CRM involvement (negative vs. positive)	**2.06 (1.22–3.47, 0.007)**	**1.66 (1.20–2.30, 0.002)**	**1.80 (1.37–2.38, <0.001)**	**1.67 (1.11–2.51, 0.014)**
Lymphovascular invasion (negative vs. positive)	0.85 (0.48–1.52, 0.584)	**1.41 (1.01–1.97, 0.043)**	1.23 (0.92–1.65, 0.156)	1.30 (0.86–1.98, 0.212)
Perineural invasion (negative vs. positive)	**2.89 (1.73–4.83, <0.001)**	**1.78 (1.32–2.42, <0.001**	**1.94 (1.49–2.52, <0.001)**	**2.43 (1.69–3.50, <0.001)**

Abbreviations: CI, confidence interval; LRFFS, locoregional failure-free survival; DFFS, distant failure-free survival; RFS, recurrence-free survival; OS, overall survival.

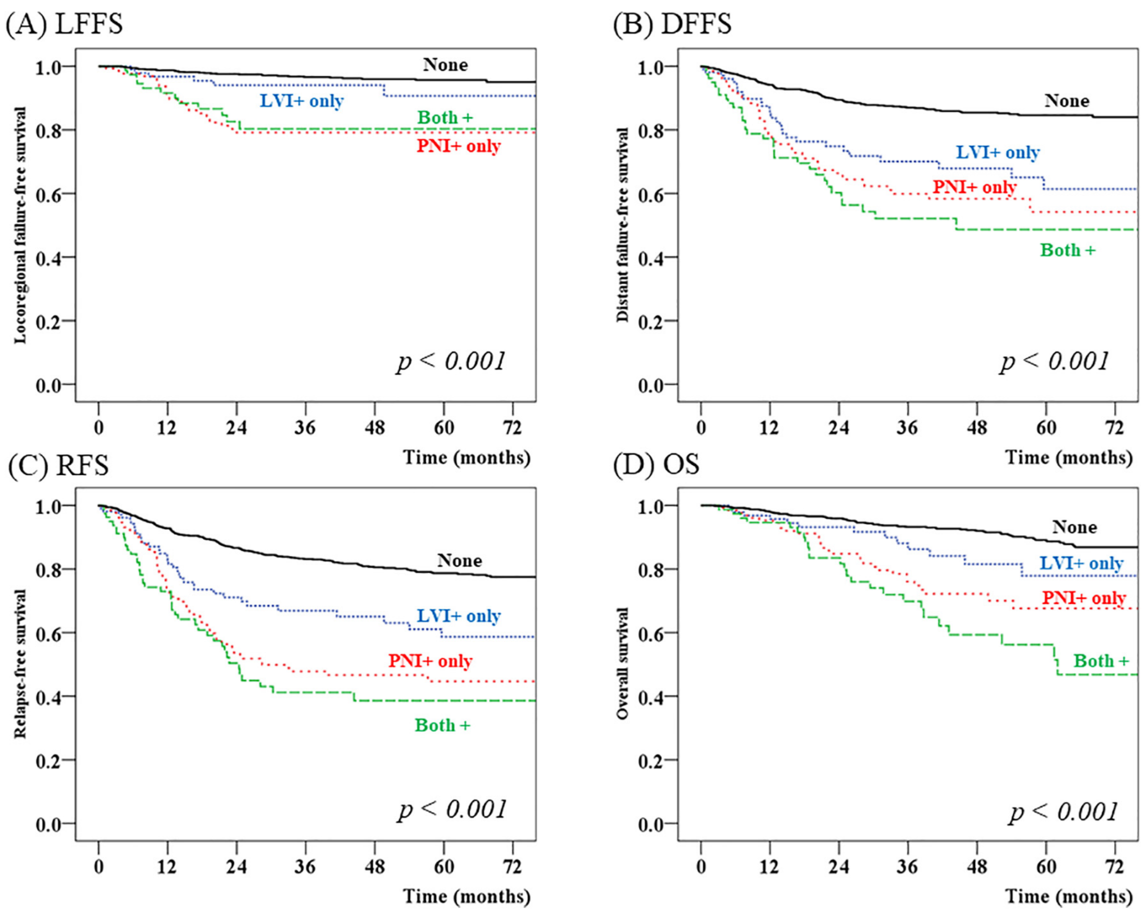

Fig. 1. The locoregional failure-free survival (LFFS), distant failure-free survival (DFFS), recurrence-free survival (RFS), and overall survival (OS) rates among subgroups divided by lymphovascular and perineural invasion status.

Significance of LVI and PNI

Fig. 1 shows LFFS, DFFS, RFS, and OS for four groups according to the status of LVI and PNI. Five-year LFFS rate was significantly lower in both-present (80.3%) and PNI+ only patients (79.2%) compared to LVI+ only (90.7%) and both-absent patients (95.7%, $p < 0.001$). However, LFFS rate was not significantly different between both-absent and LVI+ only groups ($p = 0.110$). Five-year RFS (78.7% vs. 58.7% vs. 44.6% vs. 38.6%; $p < 0.001$) and OS (89.1% vs. 77.9% vs. 67.6% vs. 56.2%; $p < 0.001$) rates at five years were significantly different among both-absent, LVI+ only, PNI+ only, and both-present groups. The 5-year DFFS rate was 84.6% in both-absent, 61.4% in LVI+ only, 54.2% in PNI+ only, and 48.6% in both-present patients. PNI+ only group showed significantly inferior results compared to LVI+ only group in LFFS, DFFS, DFS, and OS.

The effect of adjuvant chemotherapy

Table 4 shows the effect of adjuvant chemotherapy on 5-year DFFS. The 5-year DFFS rate was not significantly higher in adjuvant chemotherapy group than no adjuvant chemotherapy group (80.6% vs. 77.2%, $p = 0.805$). In the subgroup analysis of DFFS according to the receipt of adjuvant chemotherapy, there was no significant effect of adjuvant chemotherapy for subgroups classified by pathologic T and N stage and LVI status. However, adjuvant chemotherapy significantly reduced the distant failure rate in PNI+ patients. The effect of adjuvant chemotherapy according to LVI and PNI status is shown in Fig. 2. The 5-year DFFS rates were significantly different between no adjuvant chemotherapy and adjuvant chemotherapy groups in PNI+ patients (44.9% vs. 54.6%, $p = 0.048$). In the subgroup analysis, 5-FU and leucovorin regimen ($n = 153$) and FOLFOX regimen ($n = 21$) had no significant difference in 5-year DFFS (55.4% vs. 54.4%; $p = 0.371$) for PNI+ patients. The 5-year DFFS rates were not significantly different between no adjuvant chemotherapy and adjuvant chemotherapy groups in LVI+ patients (65.0% vs. 56.1%, $p = 0.487$).

Discussion

Lymphatic and vascular invasions are well known routes of metastatic cancer spread [12]. These are well characterized, and many current researches have focused on their biologic and clinical significances. However, PNI has received relatively low research attention. Its significance is usually underestimated. PNI is a distinct pathologic characteristic that can be found even without LVI. Although PNI could be simply regarded as a route of locoregional spread, it also can be the sole route of distant metastatic spread [15,16].

The exact mechanism how PNI could be a route of disease progression and distant metastasis is still unknown. Until recently, PNI was usually regarded as the spread of tumor cells passively along planes of least resistance in the connective tissues that cover the nerve sheath [15]. PNI is more like invasion than simple tumoral diffusion. Several neurotrophic factors and chemokines interact between the tumor cells and perineural microenvironments. These interactions might induce cancer aggressiveness and metastasis, and chemotherapy could impede the specific perineural spread of tumor [16].

Table 4
Subgroup analysis for the effect of adjuvant chemotherapy on 5-year distant failure-free survival.

5-year DFFS		No adjuvant chemotherapy	Adjuvant chemotherapy	Hazard ratio (95% CI)	*p*-Value
Pathologic T stage	ypT0-2 (*n* = 550)	92.9%	90.8%	1.09 (0.48–2.47)	0.838
	ypT3-4 (*n* = 682)	69.7%	66.4%	0.98 (0.67–1.44)	0.932
Pathologic N stage	ypN0 (*n* = 878)	87.8%	82.5%	1.46 (0.85–2.52)	0.167
	ypN+ (*n* = 354)	64.0%	63.4%	0.76 (0.48–1.20)	0.240
Circumferential resection margin	Negative (*n* = 1076)	83.0%	79.5%	1.10 (0.74–1.64)	0.623
	Positive (*n* = 156)	45.4%	63.8%	0.40 (0.19–0.81)	0.009
Lymphovascular invasion	Negative (*n* = 1047)	82.8%	80.8%	1.04 (0.70–1.54)	0.866
	Positive (*n* = 185)	65.0%	56.1%	0.78 (0.38–1.59)	0.487
Perineural invasion	Negative (*n* = 1021)	86.6%	81.8%	1.25 (0.79–1.98)	0.327
	Positive (*n* = 211)	44.9%	54.6%	0.59 0.35–0.98)	0.048

Abbreviations: CI, confidence interval; DFFS, distant failure-free survival.

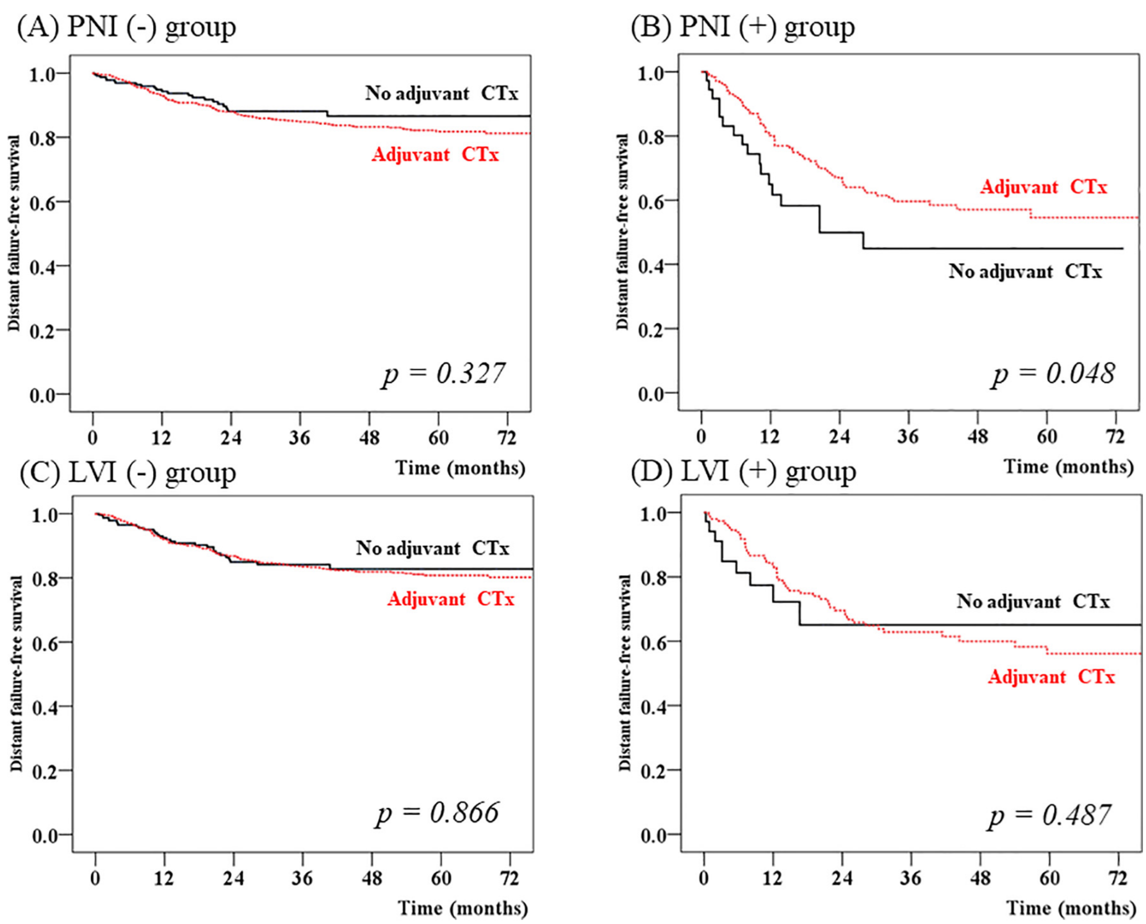

Fig. 2. The effect of adjuvant chemotherapy on distant failure-free survival (DFFS) in patients with or without perineural invasion (PNI) and lymphovascular invasion (LVI).

Some earliest clinical studies on the significance of PNI have been conducted in head and neck cancers [17,18]. This was because PNI in head and neck cancers was regarded to be a risky route for intracranial extension. This is essentially true for some cancers such as adenoid cystic carcinoma of the head and neck. In colorectal cancers, LVI has received much interest. It is regarded as an important prognostic factor for lymph node metastasis, distant metastasis, and survival. Although the definition and whether to integrate lymphatic and/or vascular invasion are different among studies, several meta-analyses have shown the prognostic significance of LVI [19].

Compared to LVI, PNI has received relatively low attention in colorectal cancers. However, recently, several studies evaluated the significance of PNI in colorectal cancer and have reported PNI as an independent prognostic factor. Kinugasa et al. analyzed 363 Dukes' B and C rectal cancer patients who did not undergo any preoperative or postoperative CRT [20]. PNI+ patients had a higher risk of disease recurrence than PNI-patients did. Van Wyk HC et al. have reviewed 38 studies and performed a meta-analysis [21]. They classified the studies into colon cancer, rectal cancer, and colorectal cancer studies. For rectal cancers, 11 studies of 3837 patients reported survival stratified by PNI. PNI was independently associated with poor survival in 7 of 11 studies. However, these included studies were heterogenous and treatment modalities were different among studies. In the current study, we included a large number of patients who were all treated by preoperative CRT followed by TME surgery. Our results showed that PNI was a poorer prognostic factor for distant metastasis compared to LVI. PNI was also an independent risk factor for locoregional recurrence, DFS, and OS whereas LVI lost its significance in multivariate analysis.

The beneficial role of adjuvant chemotherapy in rectal cancer patients treated by preoperative CRT followed by surgery remains controversial [5–9]. Many clinicians recommend adjuvant chemotherapy for stage II–III rectal cancer, assuming the same benefit for distant failure as that for colon cancer. However, the evidence is still limited. Some prospective randomized studies have failed to prove the benefit of adjuvant chemotherapy. The long-term results of the EORTC 22921 trial reported that 10-year disease-free survival rates were not different between adjuvant chemotherapy and surveillance groups (47.0% vs. 43.7%, $p = 0.290$) [5]. The phase III PROCTOR-SCRPIT trial also failed to demonstrate positive results using 5-FU based adjuvant chemotherapy (5-year OS 80.4% vs. 79.2%, $p = 0.730$), as compared to no adjuvant chemotherapy [22]. Breugom et al. have performed a meta-analysis with individual patient data acquired from four eligible trials including 1,196 rectal cancer patients [6]. Although there was no positive effect of adjuvant chemotherapy overall, in the subgroup analysis, patients with upper rectal cancer (tumor with 10–15 cm from anal verge) had benefit from adjuvant chemotherapy in terms of distant metastasis and disease-free survival (HR, 0.61, $p = 0.025$; and HR: 0.59, $p = 0.005$, respectively). However, they did not perform a subgroup analysis with postoperative pathologic features. Based on our study, we suggest that the status of PNI, not LVI could be an indicator for identifying patients who could benefit from adjuvant systemic chemotherapy. Although we could not define the optimal regimen because of the small number of patients who received adjuvant FOLFOX chemotherapy ($n = 62$). These results were similar to those of Cienfuegus et al. They analyzed a prospective database of 507 patients with stage I–II colon cancer [23]. They analyzed that PNI as a prognostic factor for disease-free survival, and the impact of PNI could be reversed by 5-FU based adjuvant chemotherapy. These clinical results could be a motivational factor to evaluate the mechanism of how PNI could be a route of distant metastasis.

Valentini et al. have used nomograms to predict local recurrence, distant metastasis, and OS in locally advanced rectal cancer based on five major European clinical trials [13]. They also tried to make a criterion for selection of patients who may benefit most from postoperative adjuvant chemotherapy. The variables used in the analysis were sex, age, clinical tumor stage, tumor location, radiotherapy dose, concurrent and adjuvant chemotherapy, surgery procedure, and ypT/N stage. In the nomogram, adjuvant chemotherapy was a significant factor for local recurrence, distant metastasis, and survival. Although PNI was not evaluated in this study, this study result showed the need for risk stratification and optimal patient selection for adjuvant chemotherapy. Further similar studies with postoperative pathologic parameters, especially such with PNI, seem to be needed in the future.

Since our study was retrospective in nature, we could not derive a statistical design to address the specific value of adjuvant treatment in rectal cancer [24]. The adjuvant chemotherapy regimen was also diverse and the patient number was limited for evaluating the effect of each regimen. There also could be intra- and inter-hospital variability in the pathologic examination since central pathologic assessment to define the presence of LVI and/or PNI was lacking in this multi-center study. However, in the present study, we included uniform patients with mid to low rectal cancer (<10 cm from anal verge) and our analyses showed that some patients with the presence of PNI and/or CRM could benefit from adjuvant systemic chemotherapy. Although pathologic T and N stage are very important both for local and distant failure, they might have no role to classify patients for delivering adjuvant systemic chemotherapy.

In conclusion, PNI is more significant than LVI for distant metastasis and survival in rectal cancer patients treated by preoperative CRT and TME surgery. Thus, the status of PNI could be an indicator for identifying patients who could benefit from adjuvant systemic chemotherapy.

Compliance with ethical standards

Authors' disclosures of potential conflicts of interest; The authors declare no funding source or other interest that is relevant to this article.

Institutional Review Board approval was obtained at each participating center before enrolling patients.

Jin Ho Song and Mina Yu equally contributed to this work.

Authors' disclosures of potential conflicts of interest

The authors declare no financial or other interest that is relevant to this article.

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