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Perineural Invasion Predicts for Distant Metastasis in Locally Advanced Rectal Cancer Treated With Neoadjuvant Chemoradiation and Surgery

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Abstract

Objectives—The benefit of adjuvant chemotherapy in patients with locally advanced rectal cancer (LARC) treated with neoadjuvant chemoradiotherapy (nCRT) and surgery is controversial. We examined the association of perineural invasion (PNI) with outcomes to determine whether PNI could be used to risk-stratify patients.

Materials and Methods—We performed a retrospective study of 110 patients treated with nCRT and surgery for LARC at our institution from 2004 to 2011. Eighty-seven patients were identified in our final analysis. We evaluated the association of PNI with locoregional control, distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival, using log-rank and Cox proportional hazard modeling.

Results—Fourteen patients (16%) were PNI + and 73 patients (84%) were PNI–. The median follow-up was 27 months (range, 0.9 to 84 mo). The median DMFS was 13.5 months for PNI + and median not reached (> 40 mo) for PNI– ($P < 0.0001$). The median DFS was 13.5 months for PNI + and 39.8 months for PNI– ($P < 0.0001$). In a multivariate model including 7 pathologic variables, type of surgery, time to surgery from end of nCRT, and use of adjuvant chemotherapy, PNI remained a significant independent predictor of DMFS (hazard ratio 9.79; 95% confidence

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interval, 3.48–27.53; $P < 0.0001$) and DFS (hazard ratio 5.72; 95% confidence interval, 2.2–14.9; $P = 0.0001$).

Conclusions—For patients with LARC treated with nCRT, PNI found at the time of surgery is significantly associated with worse DMFS and DFS. Our data support testing the role of adjuvant chemotherapy in patients with PNI and perhaps other high-risk features.

Keywords

rectal cancer; neoadjuvant therapy; chemotherapy; radiation; perineural invasion

For the past decade, the standard of care for locally advanced rectal adenocarcinoma (clinically T3-T4 and/or node positive [N +]) has been neoadjuvant chemoradiotherapy (nCRT) with a fluoropyrimidine-based chemotherapy followed by total mesorectal excision.^{1,2} After surgery, guidelines³ have traditionally recommended adjuvant chemotherapy, however, the routine use of this for all patients has been questioned over the past few years. Studies have shown that the benefit of adjuvant chemotherapy in patients treated with nCRT is unclear.^{4–6} These studies have highlighted the need for better selection of adjuvant therapy to specific subsets of patients. Thus, efforts have been made to determine the prognostic value of patient-related, treatment-related, and pathologic features to help define which patients would derive the most benefit from adjuvant therapy. One pathologic feature that has recently been suggested as a biomarker is perineural invasion (PNI).

PNI is the pathologic process of tumor invasion of nerves and spread along nerve sheaths. A widely cited and broad definition of PNI was put forth by Batsakis⁷ in his 1985 article on neurotropic carcinomas; he defined PNI as “invasion in, around, and through peripheral nerves.” Although the exact definition of PNI has varied in the literature, PNI is well established as a significant prognostic factor in head and neck cancers, and has been associated with poor outcomes in prostate, pancreas, colon, skin, and other cancers.^{8–10} Recent studies have reported on the significance of PNI in locally advanced rectal cancer (LARC) treated with nCRT. These studies have shown PNI to be one of several histopathologic variables associated with adverse clinical outcomes.^{11–13} We examined the impact of PNI in patients with LARC treated with nCRT using a multivariate analysis model to determine whether PNI is an independent variable that could be used as a prognostic biomarker to determine a patient’s risk of disease relapse and thus help inform risk stratification for the use of adjuvant therapies.

MATERIALS AND METHODS

Patient Selection

We reviewed the medical records of 110 consecutive patients with LARC (clinically T3-T4 and/or node positive [N +]) treated with nCRT followed by surgical resection from 2004 to 2011. This retrospective review was approved by the institutional review board. We collected data pertaining to demographics, staging, tumor markers, treatment, pathology, and outcomes for each patient. Twenty patients (18%) were removed from our analysis as they achieved a pathologic complete response (pCR) after nCRT and no residual tumor was found after surgery. Two patients were removed due to limited follow-up information and 1 patient

was removed due to presence of a second metastatic cancer. This left a total of 87 patients for analysis.

Staging and Treatment

Clinical staging was performed with physical exam, endoscopy, endorectal ultrasonography, abdominopelvic computed tomography, and/or magnetic resonance imaging. Tumors were staged according to American Joint Committee on Cancer (AJCC) guidelines (the majority with 6th edition,¹⁴ but after 2010 with the 7th edition¹⁵), based on tumor invasiveness, nodal involvement, and metastasis. Patients received nCRT with a 5-FU or capecitabine-based chemotherapy regimen. The majority received concurrent external beam radiation therapy to a total dose of 45 to 50.4 Gy radiation in 1.8 Gy daily fractions, 5 d/wk (for 5 to 6 wk) with a median dose of 50.4 Gy (range, 18 to 54 Gy). For patients receiving 50.4 Gy, 45 Gy in 25 fractions was delivered initially to the whole pelvis, followed by a 5.4 Gy boost in 3 fractions to the gross tumor volume plus margin. Patients underwent proctectomy consisting of total mesorectal excision 6 to 10 weeks after completion of nCRT. Three patients received intraoperative radiation therapy during surgical resection; 2 of these patients underwent total pelvic exenteration and 1 underwent low anterior resection. Overall, 47 (54%) patients had low anterior resection, 34 (39%) patients had abdominoperineal resection, 4 (5%) underwent total pelvic exenteration, and 2 (2%) had transanal excision alone. Fifty-eight patients (66%) received adjuvant chemotherapy with a 5-FU or capecitabine-based regimen after surgery. Patients received follow-up and restaging scans per the treating physician and team.

Pathologic Analysis

Pathologists specializing in colorectal cancer at our institution examined the surgical specimens using AJCC criteria^{14,15} described above to assess response to neoadjuvant therapy. Features examined included pCR, pathologic T and N stages, histologic grade, number of lymph nodes, extranodal extension, tumor size, PNI, lymphovascular space invasion, circumferential (radial) margins, distal margins, as well as other features included in the standard reporting protocol for rectal cancer specimens as determined by the College of American Pathologists.^{16,17} At our institution, PNI is defined as the presence of neoplastic cells in the perineural space and it is identified using hematoxylin and eosin staining (Figs. 1A, B).

Statistical Analysis

The differences in patient characteristics between PNI + and PNI- patients were compared using the χ^2 test for categorical variables and the 2-sample *t* test for continuous variables. For each patient, locoregional control (LRC) and distant metastasis-free survival (DMFS) were defined as the time from the date of diagnosis to the corresponding date of local/distant disease recurrence or death from any cause; disease-free survival (DFS) was defined as time to the date of any relapse or death, whichever occurred first; overall survival (OS) was defined as time from date of diagnosis to the date of death. Patients who were disease-free and alive at the last follow-up were censored at the last follow-up date. Patients with disease recurrence but alive at the last follow-up were censored at the last follow-up date for OS analysis only. Univariate analyses of variables associated with DMFS and DFS were conducted using Kaplan-Meier survival analysis and log-rank tests. Multivariate survival

analysis of variables associated with DMFS and DFS were performed using Cox proportional hazard modeling with a stepwise variable selection process where the significance level of a variable to enter the model was 0.25 and to stay in the model was 0.15. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

The median follow-up time of our cohort of 87 patients was 27 months (range, 0.9 to 84 mo). Thirty-four (39%) patients were female and 53 (61%) were male. The median age was 59 years (range, 22 to 81 y). We divided patients into 2 groups based on whether PNI was identified in the surgical pathologic specimen (PNI + vs. PNI-). Of the 87 patients, 14 patients (16%) were PNI + and 73 patients (84%) were PNI-. The demographic and treatment-related characteristics of these 2 groups are shown in Table 1. There were no significant differences in sex, age at diagnosis, the number of patients diagnosed at ≤ 70 versus >70 years, pretreatment carcinoembryonic antigen level, clinical T stage, clinical N stage, or biopsy grade between the 2 groups. Likewise, there were no significant differences in treatment-related characteristics including: dose of neoadjuvant radiation, type of surgery, time to surgery from end of nCRT, or the percent of patients receiving adjuvant chemotherapy.

Pathologic Characteristics After Neoadjuvant Chemoradiation

Pathologic features from the rectal cancer specimens of our study population are shown in Table 2. There were no statistically significant differences between PNI + and PNI- patients with regard to the following variables: maximum tumor size (≤ 3 vs. >3 cm), lymphovascular space invasion (LVSI), extramural venous invasion (EVI), LVSI and EVI combined, distal margin of resection, and tumor distance from the anal verge. We did observe a statistically significant difference between the 2 groups with regard to pathologic T (pT) stage. Eighty-six percent (12/14) of patients in the PNI + group had a pT stage of 3 to 4 versus 52% (38/73) of patients in the PNI- group ($P = 0.025$). In addition, there was a trending association ($P < 0.1$) between the presence of PNI and worse pathologic N (pN) stage, histologic grade, and radial (circumferential) margin of resection.

Survival and Outcomes

Of the 87 patients in our analysis, 14 patients died (from any cause) during the analysis period: 3 of 14 patients (21%) were in the PNI + group, and 11 of 73 patients (15%) were in the PNI- group. The median OS was 55.4 months for PNI + patients and 83.6 months for PNI- patients ($P = 0.15$). Regarding locoregional control (LRC), 2 of 14 patients (14%) recurred locoregionally in the PNI + group, and 11 of 73 patients (15%) recurred local regionally in the PNI- group. The median LRC was not reached for PNI + and PNI- patients ($P = 0.71$). For the outcome of distant metastasis, 10 of 14 patients (71%) in the PNI + group had distant metastasis, whereas 16 of 73 patients (22%) in the PNI- group had distant metastasis. The median DMFS was 13.5 months for PNI + patients and median not reached (> 40 mo) for PNI- patients ($P < 0.0001$) (Fig. 2A). For DFS, 10 of 14 patients

(71%) in the PNI + group had disease recurrence, whereas 23 of 73 patients (31%) in the PNI– group had disease recurrence. The median DFS was 13.5 months for PNI + patients and 39.8 months for PNI– patients ($P < 0.0001$) (Fig. 2B).

PNI as a Prognostic Factor on Univariate Analysis

Univariate analyses were conducted to evaluate the prognostic significance of PNI as well as other pathologic, clinical, and treatment-related variables, including: cT stage, cN stage, biopsy grade, pT stage, pN stage, histologic grade, radial margin status, LVSI/EVI, tumor distance from the anal verge, type of surgery, time to surgery from end of nCRT, and use of adjuvant chemotherapy after surgery (Table 3). In our univariate analysis, the presence of PNI was significantly associated with worse DFS (hazard ratio [HR] 6.07; 95% confidence interval [95% CI], 2.69–13.71; $P < 0.0001$) and DMFS (HR 7.36; 95% CI, 3.15–17.19; $P < 0.0001$). Likewise, patients with a pT stage of 3 to 4 had worse DFS (HR 3.99; 95% CI, 1.62–9.81; $P = 0.0026$) and DMFS (HR 3.44; 95% CI, 1.29–9.16; $P = 0.014$). In addition, patients with a pN stage of 1 to 2 compared with a pN stage of 0 also had worse DFS (HR 2.55; 95% CI, 1.21–5.36; $P = 0.014$) and DMFS (HR 3.84; 95% CI, 1.54–9.59; $P = 0.0039$). The other variables evaluated in our univariate analysis showed no association with either DFS or DMFS.

With regard to the outcome of LRC, we found no difference between PNI + and PNI– groups (HR 1.33; 95% CI, 0.29–6.16; $P = 0.71$). In addition, we were unable to detect a statistically significant difference between the 2 groups when considering OS, perhaps due to limited data as a result of censoring, short follow-up, and few observed events (HR 2.63; 95% CI, 0.70–9.82; $P = 0.15$).

PNI as an Independent Prognostic Factor on Multivariate Analysis for DFS and DMFS

Multivariate survival analyses using Cox regression modeling and a stepwise selection procedure to evaluate the impact of PNI and other relevant covariates on DFS and DMFS included the following variables: PNI, pT stage, pN stage, histologic grade, LVSI/EVI, tumor distance from the anal verge, radial margin status, type of surgery, time to surgery from end of nCRT, and use of adjuvant chemotherapy (Table 3). In the final selected multivariate model, PNI remained significantly and independently associated with DFS (HR 5.72; 95% CI, 2.2–14.9; $P = 0.0001$) and DMFS (HR 9.79; 95% CI, 3.48–27.53; $P < 0.0001$). pN stage also remained an independent prognostic factor for DFS (HR 2.61; 95% CI, 1.05–6.51; $P = 0.0393$) and DMFS (HR 6.02; 95% CI, 1.97–18.43; $P = 0.0017$). Notably, higher pT stage did not emerge as an independent prognostic factor for either DFS or DMFS in the multivariate analysis, although there was a trending association between higher pT stage and DFS (HR 2.51; 95% CI, 0.88–6.51; $P = 0.0839$). Thus, although there were a significantly higher number of pT3-4 tumors in the PNI + group (86%, $n = 12/14$) compared with the PNI– group (52%, $n = 38/73$) ($P = 0.025$), this imbalance in pT stage did not account for the observed outcomes.

DISCUSSION

In this study, we assessed the value of PNI as a pathologic feature that could be used to identify patients at high risk for poor outcomes. In the PNI + and PNI– groups, there were no significant differences in demographic or treatment-related variables, and of the pathologic variables examined, the only significant difference was in pT stage ($P = 0.025$) (Tables 1 and 2). In our univariate analysis, we evaluated 13 variables, out of which PNI, pT stage, and pN stage were significantly associated with DFS and DMFS (Table 3). In our multivariate model, PNI and pN stage remained significant for both DFS and DMFS (Table 3). Notably, pT stage was only trending for DFS, and did not remain significant for DMFS. Thus, although the PNI + group had a greater number of pT3-4 tumors (86%, $n = 12/14$) than the PNI– group (52%, $n = 38/73$), this difference did not account for the worse outcomes observed in the PNI + group. Rather, PNI and pN stage emerged as the strongest independent factors driving clinical outcomes.

A number of studies in the past decade have discussed PNI as a significant prognostic indicator in LARC. The major limitations of these studies include: (1) patients being treated with primary resection rather than nCRT followed by surgery¹⁸; (2) PNI being investigated in a mixed population of patients receiving primary resection and nCRT¹⁹; and (3) the presence of missing data on PNI resulting in many patients with unknown PNI status.²⁰ In Table 4, we have summarized the prior studies most relevant to ours.

Table 4 displays 10 studies, including ours, all of which are retrospective. In each study, patients with LARC were treated with nCRT and surgery. The percent of patients with PNI in the 9 other studies ranged from 8.3% to 27.3% (median, 18.8%), which is consistent with our observed PNI rate of 16% ($n = 14/87$). Six studies in addition to ours found PNI to be significant for DFS on multivariate analysis.^{11–13,23,24,26} Of note, PNI was combined with lymphovascular invasion (LVI) as a single variable in the multivariate analysis in 2 studies.^{11,26} Also, 2 studies did not find PNI to be correlated with DFS on multivariate analysis^{22,25}; however, in one of these studies,²⁵ PNI was correlated with DFS on univariate analysis ($P < 0.001$), and the P -value was close to being significant ($P = 0.051$) on multivariate analysis. The findings on DFS from our analysis are largely consistent with the findings reported in these studies.

Regarding the outcome of DMFS, 2 studies reported a correlation between PNI and distant metastasis; this correlation was found on both univariate ($P < 0.001$; $P < 0.001$) and multivariate ($P = 0.008$; $P = 0.002$) analyses.^{12,21} This finding is consistent with our study, as we found a correlation between PNI and worse DMFS in both univariate ($P < 0.0001$) and multivariate ($P < 0.0001$) analyses. The other 7 studies did not report on an association between PNI and DMFS specifically, highlighting the relative novelty of our findings.

The findings from the studies in Table 4 for the association of PNI with OS were more conflicting than the findings for DFS and DMFS. Four studies reported a significant correlation between PNI and OS on multivariate analysis^{11–13,26}; however, 2 of these studies performed this analysis on PNI and/or LVI as a combined variable.^{11,26} Two studies found no impact of PNI on OS in multivariate analysis, although both found an impact of PNI on

OS in univariate analysis, and both studies evaluated PNI as a single variable not combined with LVI.^{24,25} In our study, we may not have been able to fully evaluate the impact of PNI on OS due to censoring of patients, limited follow-up, and few observed events ($P = 0.15$).

There is limited evidence for an association of PNI with LRC. Only 1 study in Table 4 found a significant impact of PNI on local recurrence; this was in both univariate ($P < 0.001$) and multivariate analyses ($P = 0.012$).²¹ The 2 other studies in Table 4 that evaluated the impact of PNI on LRC did not find a significant association between PNI and this outcome.^{12,22} Similarly, in our study, we found no correlation between PNI and LRC ($P = 0.71$). This is likely due to high rates of LRC achieved with trimodality therapy. As there was no difference in LRC between the PNI + and PNI- groups in our study, the difference observed in DFS was likely driven by earlier development of metastasis in the PNI + group.

The most compelling arguments from the studies shown in Table 4 and our study are associations between PNI and DFS and PNI and DMFS. One of the strengths of our study in particular is that we performed our statistical analyses on PNI as a separate variable from LVI, unlike some of the other studies discussed here.^{11,26} Although PNI and LVI are both adverse pathologic features, they represent distinct pathologic processes. Interestingly, Huang et al¹² found that patients who were both PNI + and ypN + had a significantly lower DFS ($P < 0.001$) and OS ($P < 0.001$) compared with patients exhibiting the other 3 phenotypes (PNI-/ypN-, PNI+/ypN-, and PNI-/ypN+). We found similar results, with patients who were both PNI + and pN + (10/87) having a significantly lower DFS ($P < 0.001$) and DMFS ($P < 0.001$) than patients with the other 3 phenotypes (77 of 87) (Supplemental Figures 1A and 1B, Supplemental Digital Content 1, <http://links.lww.com/AJCO/A106>).

As mentioned above, the use of adjuvant chemotherapy after nCRT for LARC is controversial and therapy selection is not driven by the presence of high-risk profiles.^{4-6,27} In fact, no randomized clinical trial in LARC has demonstrated a significant difference in DFS or OS when adjuvant chemotherapy is given after nCRT and surgery. Each of the following trials showed no benefit to adjuvant chemotherapy: the EORTC 22921 trial ($n = 1011$),^{28,29} the Italian trial (Sainato et al; $n = 655$),³⁰ the PROCTOR/SCRIPT trial ($n = 470$),³¹ and the Chronicle trial ($n = 113$).³² In addition, none of these studies reported the incidence of PNI in the treatment arms or evaluated the relationship of PNI with outcomes. Not surprisingly, in the 10 studies shown in Table 4 including ours, there was considerable variation in the percent of patients receiving adjuvant chemotherapy and the regimens used. The number of patients receiving adjuvant therapy ranged from 53.7% to 100%, with the studies having different criteria for the use of adjuvant therapy. In an effort to guide more judicious use of adjuvant therapy, some centers have come up with prognostication scoring systems that take into account various patient/treatment-related characteristics and pathologic features of the tumor. In the "Nottingham Rectal Cancer Prognostic Index" (NRPI) recently proposed by Dhadda et al,¹³ the NRPI (which included PNI as a variable) was found to be significantly more powerful than current AJCC staging in predicting both DFS (NRPI $P = 0.001$; AJCC $P = 0.019$) and OS (NRPI $P < 0.0001$; AJCC $P = 0.928$). In another nomogram to predict pathologic nodal status after nCRT recently proposed by Jwa et al,³³ PNI is included as 1 of 6 variables. Although this nomogram is intended to predict

the probability of lymph node metastasis and not long-term clinical outcomes, the underlying concept of attempting to identify “high-risk” patients is similar. Our study adds to the current literature by lending further evidence for the prognostic value of both PNI and PNI and pN + combined in defining risk profiles for patients with rectal adenocarcinoma treated with nCRT. Regardless of whether a formal prognostication system is used, PNI and pN stage have been shown to be independent predictors of outcomes and should be considered in the stratification of patients for risk of recurrence. Furthermore, our study underscores the importance of accurate reporting on the presence or absence of PNI in residual rectal cancer specimens. Although PNI is part of the standard reporting protocol for rectal cancer specimens as recommended by the College of American Pathologists,¹⁷ it is not universally reported.

One of the main limitations of this study is its retrospective design, and therefore we were not able to control for the heterogeneity of the treatment delivered, including the dosing of preoperative radiation, and the dosing/schedule of preoperative and adjuvant chemotherapy. Furthermore, there may have been potential interevaluator differences in the review and characterization of pathologic specimens. It is also possible that there was under-reporting of PNI in the rectal cancer specimens. In addition, tumor regression grade (TRG) is a pathologic feature that should be reviewed in future studies and evaluated as a prognostic factor for outcomes, as it has received recent attention as a prognostic factor in LARC treated with nCRT.³⁴ Unfortunately, as TRG was added to the rectal cancer reporting criteria in the AJCC 7th edition (2010), and most of our patients were treated before 2010, we did not have sufficient cases to evaluate the prognostic impact of TRG. Finally, the 20 patients with pCR were not included in this study as our intention was to focus more directly on the prognostic impact of PNI on patients with *residual* tumor at the time of surgery. Including patients with pCR into our non-PNI group would have likely biased the analysis in favor of non-PNI group with regards to outcomes, given the established favorable prognostic impact for patients who achieve pCR.

In summary, PNI and pN + stage are strongly and independently associated with DFS and DMFS in patients with LARC treated with nCRT followed by surgery. Because PNI, pN + stage, and the combination of both together are “high-risk” features, patients demonstrating these features could perhaps be considered for therapy intensification. However, prospective trials are needed to determine whether patients with high-risk profiles, including PNI, pN +, and other prognostic biomarkers, benefit from adjuvant chemotherapy after nCRT and surgery for LARC. To our knowledge, there have been no such prospective trials aimed at these high-risk patients. Nevertheless, this study highlights that in locally advanced rectal cancer, there are specific subsets of patients with more aggressive phenotypes, whose plan of care after nCRT and surgery needs to be further optimized.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Histologic microphotograph of perineural invasion in rectal adenocarcinoma (hematoxylin and eosin stain). A, Rectal adenocarcinoma composed of irregular glands (arrowheads) invading perineural space (arrow), $\times 200$. B, Higher power showing the malignant gland wrapping around the nerve (arrows), $\times 400$.

FIGURE 2.

A, Distant metastasis-free survival (DMFS) between PNI + and PNI- groups. The median DMFS was 13.5 months for PNI + patients and median not reached (> 40 mo) for PNI- patients (log rank $P < 0.0001$). B, Disease-free survival (DFS) between PNI + and PNI- groups. The median DFS was 13.5 months for PNI + patients and 39.8 months for PNI- patients (log rank $P < 0.0001$).

TABLE 1

Demographic, Clinical, and Treatment-related Characteristics of PNI + and PNI– Groups

Characteristic	PNI+, n = 14 (16%)	PNI–, n = 73 (84%)	P
Median follow-up (range) (mo)	21 (13–55)	28 (0.9–84)	
Sex (n [%])			0.75
Female	6 (43)	28 (38)	
Male	8 (57)	45 (62)	
Median age at diagnosis (range) (y)	60 (22–78)	59 (27–81)	0.89
Age at diagnosis			0.43
70	13 (93)	62 (85)	
> 70	1 (7)	11 (15)	
Pretreatment CEA (ng/mL)			0.311
5	4 (29)	30 (41)	
> 5	5 (36)	18 (25)	
Unknown	5 (36)	25 (34)	
Radiation dose (Gy)			0.48
50.4	8 (57)	53 (73)	
> 50.4	4 (29)	12 (16)	
Unknown	2 (14)	8 (11)	
Surgery type			0.12 [^]
LAR	5 (36)	42 (58)	
APR	8 (57)	26 (36)	
TPE	1 (7)	3 (4)	
TAE		2 (3)	
Adjuvant chemotherapy			0.73
Yes	9 (64)	49 (67)	
No	2 (14)	14 (19)	
Unknown	3 (21)	10 (14)	
Time to surgery from end of nCRT (median = 7 wk) (wk)			0.63
7	5 (36)	36 (49)	
> 7	7 (50)	30 (41)	
Unknown	2 (14)	7 (10)	
Clinical T stage			0.21
1–2	1 (7)	2 (3)	
3–4	13 (93)	59 (81)	
Unknown		12 (16)	
Clinical N stage			0.52
N0	8 (57)	41 (56)	
N +	6 (43)	26 (36)	
Unknown		6 (8)	
Biopsy grade			0.2
1	1 (7)	9 (12)	

Characteristic	PNI+, n = 14 (16%)	PNI-, n = 73 (84%)	P
2	7 (50)	45 (62)	
3	1 (7)	0 (0)	
Unknown	5 (36)	19 (26)	

[^]
P-value compares LAR and APR.

APR indicates abdominoperineal resection; CEA, carcinoembryonic antigen; LAR, low anterior resection; nCRT, neoadjuvant chemoradiotherapy; PNI, perineural invasion; TAE, transanal excision; TPE, total pelvic exenteration.

TABLE 2

Pathologic Features After Neoadjuvant Chemoradiation of PNI + and PNI– Groups

Characteristic	PNI +, n = 14 (16%)	PNI–, n = 73 (84%)	P
pT stage			0.025
1–2	2 (14)	33 (45)	
3–4	12 (86)	38 (52)	
Unknown		2 (3)	
pN stage			0.071
N0	4 (29)	39 (53)	
N +	10 (71)	32 (44)	
Unknown		2 (3)	
Maximum tumor size (cm)			0.91
3	8 (57)	40 (55)	
> 3	6 (43)	28 (38)	
Unknown		5 (7)	
Histologic grade			0.097
Low (1–2)	11 (79)	65 (89)	
High (3)	3 (21)	5 (7)	
Unknown		3 (4)	
LVI			0.81
Yes	1 (7)	4 (5)	
No	13 (93)	69 (95)	
EVI			0.31
Yes	0 (0)	5 (7)	
No	14 (100)	68 (93)	
LVI or EVI			0.58
Yes	1 (7)	9 (12)	
No	13 (93)	64 (88)	
Tumor distance from anal verge (cm)			0.3
5	6 (43)	17 (23)	
> 5	4 (29)	31 (43)	
Unknown	4 (28)	25 (34)	
Distal margin			0.26
Positive/close *	2 (14)	4 (6)	
Negative	12 (86)	65 (89)	
Unknown		4 (5)	
Radial margin			0.056
Positive/close *	5 (36)	11 (15)	
Negative	8 (57)	59 (81)	
Unknown	1 (7)	3 (4)	

* Close margin is 0.2 cm.

EVI indicates extramural venous invasion; LVI, lymphovascular invasion; pN, pathologic N; PNI, perineural invasion; pT, pathologic T.

TABLE 3

Univariate and Multivariate Analysis of PNI and Select Variables for Disease-free Survival (DFS) and Distant Metastasis-free Survival (DMFS)

	Univariate Analysis			
	DFS		DMFS	
	HR (95% CI)	P	HR (95% CI)	P
PNI				
Yes vs. no	6.07 (2.69–13.71)	<0.0001	7.36 (3.15–17.19)	<0.0001
pT stage				
3–4 vs. 1–2	3.99 (1.62–9.81)	0.0026	3.44 (1.29–9.16)	0.014
pN stage				
N + vs. N0	2.55 (1.21–5.36)	0.014	3.84 (1.54–9.59)	0.0039
Histologic grade				
3 vs. 1–2	1.25 (0.44–3.56)	0.68	1.78 (0.61–5.19)	0.29
Radial margin				
Positive/close vs. negative	1.36 (0.61–3.02)	0.46	1.34 (0.53–3.35)	0.54
LVI or EVI				
Yes vs. no	1.08 (0.42–2.81)	0.87	1.05 (0.40–2.75)	0.92
Tumor distance from anal verge				
5 vs. >5 cm	1.19 (0.47–3.03)	0.72	1.11 (0.40–3.05)	0.85
Surgery type				
APR vs. LAR	1.39 (0.68–2.85)	0.37	1.41 (0.63–3.14)	0.41
Adjuvant chemotherapy				
No vs. yes	1.76 (0.74–4.16)	0.20	1.64 (0.65–4.17)	0.30
Time to surgery from end of nCRT				
> 7 vs. ≤ 7 wk	1.59 (0.76–3.31)	0.22	1.45 (0.63–3.38)	0.38
Clinical T stage				
3–4 vs. 1–2	0.57 (0.08–4.29)	0.59	0.47 (0.06–3.58)	0.47
Clinical N stage				
N + vs. N0	1.27 (0.64–2.54)	0.50	1.56 (0.72–3.38)	0.26
Biopsy grade				
2–3 vs. 1	4.58 (0.61–34.1)	0.14	3.20 (0.42–24.1)	0.26
Multivariate Analysis*				
PNI				
Yes vs. no	5.72 (2.2–14.91)	0.0001	9.79 (3.48–27.53)	<0.0001
pT stage				
3–4 vs. 1–2	2.51 (0.88–6.51)	0.0839	—	—
pN stage				
N + vs. N0	2.61 (1.05–6.51)	0.0393	6.02 (1.97–18.43)	0.0017

* The first 10 variables shown in the univariate analysis table (“PNI” to “Time to surgery from end of nCRT”) were included in the selection procedure for the multivariate model.

Bold signifies that the *P*-value was deemed significant with a cut-off for significance of *P* < 0.05.

APR, abdominoperineal resection; CI, confidence interval; EVI, extramural venous invasion; LAR, low anterior resection; LVI, lymphovascular invasion; nCRT, neoadjuvant chemoradiotherapy; pN, pathologic N; PNI, perineural invasion; pT, pathologic T.

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Association of Perineural Invasion With Clinical Outcomes in Locally Advanced Rectal Cancer Treated With nCRT and Surgery: Review of Relevant Studies

TABLE 4

References	n (%)		Median F/U (mo)	LRC	DFS	DMFS	OS	Comments
	n	With PNI	Receptient of Adjuvant Chemotherapy					
Present study (OSU)	87	14 (16)	58 (66)	UV; <i>P</i> = 0.71	UV; <i>P</i> < 0.0001 MV; <i>P</i> = 0.0001	UV; <i>P</i> < 0.0001 MV; <i>P</i> < 0.0001	UV; <i>P</i> = 0.15	
Yoon et al ²¹	261 [^]	60 (23)	261 (100)	UV; <i>P</i> < 0.001 MV; <i>P</i> = 0.012	NR	UV; <i>P</i> < 0.001 MV; <i>P</i> = 0.002	NR	^13 patients were staged T2N0M0 before nCRT
Cienfuegos et al ¹¹	324	68 (20.4) [PNI/ LVI, 92 (29)]	174 (53.7)	NR	UV; <i>P</i> < 0.05* MV; <i>P</i> < 0.001*	NR	UV; <i>P</i> < 0.05* MV; <i>P</i> < 0.001*	*PNI/LVI evaluated as a combined variable
Huang et al ¹²	88	24 (27.3)	88 (100)	UV; <i>P</i> = 0.469 MV; <i>P</i> = 0.278	UV; <i>P</i> < 0.05 MV; <i>P</i> = 0.032	UV; <i>P</i> < 0.001 MV; <i>P</i> = 0.008	UV; <i>P</i> < 0.05 MV; <i>P</i> = 0.043	
Dhadda et al ¹³	158	28 (18)	156 (99)	NR	UV; <i>P</i> < 0.05 MV; <i>P</i> < 0.001	NR	UV; <i>P</i> < 0.05 MV; <i>P</i> < 0.05	
Sannier et al ²²	113	22 (19.5)	Not reported	UV; <i>P</i> < 0.1*	UV; <i>P</i> < 0.1 MV; <i>P</i> = 0.702	NR	NR	*PNI/LVI evaluated as a combined variable
Agarwal et al ²³	251	26 (10.4)	222 (88.4)	NR	UV; <i>P</i> < 0.05 MV; <i>P</i> < 0.05	NR	NR	
Lee et al ²⁴	328	66 (20.1)	328 (100)	NR	UV; <i>P</i> = 0.021 MV; <i>P</i> = 0.046	NR	UV; <i>P</i> = 0.038 MV; <i>P</i> = 0.08	
Lim et al ²⁵	581	48 (8.3)	574 (98.8)	NR	UV; <i>P</i> < 0.001 MV; <i>P</i> = 0.051	NR	UV; <i>P</i> = 0.029 MV; <i>P</i> = 0.988	
Guillem et al ²⁶	297	27 (9)	255 (86)	NR	UV; <i>P</i> < 0.001* MV; <i>P</i> < 0.001*	NR	UV; <i>P</i> < 0.001 MV; <i>P</i> < 0.001*	*PNI/LVI evaluated as a combined variable

P-values in bold are significant for outcome (*P* < 0.05).

DFS indicates disease-free survival; DMFS, distant metastasis-free survival; F/U, follow-up; LRC, locoregional control; LVI, lymphovascular invasion; MV, multivariate analysis; nCRT, neoadjuvant chemoradiotherapy; NR, no outcome reported in paper; OS, overall survival; OSU, The Ohio State University; PNI, perineural invasion; UV, univariate analysis.