Original Article

Perineural invasion is a prognostic factor in stage II colorectal cancer but not a treatment indicator for traditional chemotherapy: a retrospective cohort study

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Background: Perineural invasion (PNI) is considered a risk factor of survival but does not yet inform treatment decisions, and has not been studied separately in stage II colorectal cancer (CRC) patients whose postoperative traditional chemotherapy is controversial. This cohort study aimed to assess the association of PNI with basic clinicopathological features and patient outcomes after curative resection and the effects of PNI on responses to adjuvant chemotherapy in stage II CRC.

Methods: The clinical data of 371 stage II CRC patients who underwent curative-intent surgery at the National Cancer Center/Cancer Hospital in 2014 were retrospectively reviewed. The adjuvant chemotherapy data were acquired from follow-up information. PNI status was examined, and the overall survival (OS) and disease-free survival (DFS) rates were analyzed.

Results: PNI was detected in 82 of the 371 patients (22.1%) and was closely correlated with preoperative serum carcinoembryonic antigen (CEA) levels (P=0.030), gross tumor type (P=0.010), tumor differentiation (P=0.010), p stage (P<0.001), and extramural vascular invasion (EMVI) (P<0.001). The median follow-up time was 71 months. The 5-year OS was 84.1% and 96.5% (P<0.001), and the 5-year DFS was 75.6% and 91.3% (P<0.001) for PNI-positive (+) and PNI-negative (–) patients, respectively. The multivariate regression analyses identified PNI as an independent negative prognostic factor for DFS [hazard ratio (HR): 2.95; 95% confidence interval (CI), 1.546–5.626; P=0.001] and OS (HR: 3.966; 95% CI, 1.642–9.575; P=0.002). Among PNI (+) patients, DFS and OS were positively correlated with CEA levels (P=0.005 and P=0.004, respectively). Postoperative chemotherapy failed to improve DFS (P=0.480 and P=0.267, respectively) and OS (P=0.940 and P=0.077, respectively) regardless of whether the patients were PNI positive or not.

Conclusions: In stage II CRC patients, PNI was a poor independent predictor for DFS and OS. Among PNI (+) patients, CEA levels were positively correlated with DFS and OS. Traditional postoperative adjuvant chemotherapy does not improve outcomes of PNI (+) patients. Therefore, as to the active role of PNI and vacancy for treatment in allusion to PNI, follow-up of PNI (+) patients with elevated CEA level should be strengthened and further research on drug conducted on PNI deserve to be carried on.

Keywords: Colorectal cancer (CRC); perineural invasion (PNI); postoperative adjuvant chemotherapy

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Introduction

With 1,148,515 newly diagnosed patients and 576,858 deaths worldwide in 2020, colorectal cancer (CRC) was the 3rd most commonly diagnosed cancer and the 2nd leading cause of cancer death (1). In total, 24% of all the newly diagnosed cases and 30% of the cancer-related deaths were reported in China (2). In China, the incidence of CRC has increased rapidly, and CRC represents one of the highest burdens of cancer globally.

Tumor-node-metastasis (TNM) staging is considered the most robust predictor of outcomes and the primary guidance for the subsequent therapy of patients with CRC. Stage II CRC accounts for approximately 25% of all CRC cases (3), and approximately 15–25% of patients relapse or die within 5 years of radical surgery (4). For primary curative CRC, adjuvant chemotherapy is inappropriate for stage I patients and considered the standard treatment for stage III patients under the National Comprehensive Cancer Network guidelines. However, the benefits of adjuvant chemotherapy for stage II patients remain controversial. Thus, supplemental pathological features are indispensable to further stratify the risk of stage II CRC.

The criteria for adjuvant therapy for patients with stage II CRC is the presence of any one of the following high risk factors including poor differentiation, emergency surgery, fewer than 12 examined lymph nodes, the presence of extramural vascular invasion (EMVI), perforation or a pT4 tumor (5). Apart from tumor and nodal stage, carcinoembryonic antigen (CEA) level, tumor regression grade, and surgical margin status, and perineural invasion (PNI) have been reported as prognostic factors for CRC (6). PNI is considered a risk factor of survival and has been included in the TNM Supplement for CRC since 2001 (7). However, PNI does not yet inform treatment decisions. As one of markers of risk factors, PNI plays an important role in tumor growth and progression by multiple signal pathways influencing interactions among tumors and nerves (8). However, people payed not enough attention to it, leading to recurrence of quite a lot of stage II CRC patients. Moreover, the clinicopathological factors associated with PNI and significance of postoperative traditional chemotherapy on PNI have not been studied separately in stage II CRC patients whose postoperative treatment is still controversial.

In this study, we examined the association of PNI with basic clinicopathological features and outcomes in stage II CRC patients after curative resection. We also evaluated the factors positively correlated with DFS and OS in PNI-positive (+) patients and estimated the effects of PNI on patients' responses to adjuvant chemotherapy. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-277/rc).

Methods

Patients

The clinical data of 371 stage II CRC patients who underwent curative-intent surgery at the National Cancer Center/Cancer Hospital in 2014 were retrospectively reviewed. The patients' clinical information was carefully collected from their medical records. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) have TNM stage II CRC as confirmed by a pathological report; (II) have been treated with curative complete mesocolic excision (CME) and total mesorectal excision (TME) surgery; and (III) have no evidence of distant metastasis. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had recurrent disease; (II) had synchronous and metachronous multiple cancers; (III) had multiple primary tumors within the colorectum; (IV) had hereditary non-polyposis CRC or familial adenomatous polyposis; (V) had no PNI records; (VI) had only been treated by local resection; (VII) had received presurgical chemo- or radiation therapy; (VIII) and patients missing clinical data. Our study was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (the approval number: 21/13902810). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was taken from all the patients.

Curative-intent surgery was defined as follows: (I) an absence of a gross residual tumor in the surgical bed; and (II) pathologically negative proximal and distal resection margins in terms of tumor invasion. The surgical approach was uniformly mesenteric-based CME or TME. The surgical pathology specimens were evaluated by at least 3 specialized colorectal pathologists at our Center. Clinicopathological staging was assessed according to the American Joint Commission on Cancer/Union for International Cancer Control TNM staging system (2017, 8th ed.). All patients were proven to suffer from TNM

stage II CRC. The clinicopathological features included (I) tumor size, (II) gross type, (III) pathological cell type, (IV) invasion depth, (V) lymph node involvement, (VI) histologic grade, (VII) differentiation, (VIII) resection margin, (IX) EMVI, (X) PNI, and (XI) microsatellite instability (MSI) status. PNI was assessed as positive when tumor cells were observed inside any layer of the nerve sheath or when at least 33% of the nerve periphery was surrounded by tumor cells. EMVI was assessed as positive when tumor cells were observed within an endothelium-lined vessel beyond the muscularis propria. This is a retrospective cohort study with selection bias.

Follow up

The follow-up data were acquired by outpatient reexaminations and telephone interviews. All patients were scheduled to receive follow-up outpatient visits or telephone interviews every 3 months for the first 2 years and then every 6–12 months for the next 3 years. Routine examinations included contrast-enhanced computed tomography imaging of the thorax, abdomen, and pelvis, blood tests of tumor markers every 3 months, and colonoscopies every 6 months. Overall survival (OS) time was defined as the time interval from the day of surgery to the date of last follow-up or death from any cause. Disease-free survival (DFS) time was defined as the time from the day of surgery to the day of local recurrence and/or metastases. The endpoints of this study were 5-year OS and DFS.

Statistical analysis

The relationships between PNI positivity and other clinicopathological variables were assessed using the chi-square test and Student's *t*-test (the categorical variables were analyzed using the chi-square test, and the continuous variables were analyzed using Student's *t*-test). The effects of PNI on OS and DFS were estimated using the Kaplan-Meier method and compared using a log-rank test. To identify the factors that independently affected OS and DFS, the hazard ratio (HR) with a 95% confidence interval (CI) was computed using a univariate Cox proportional-hazards regression model. Next, the predictive value of PNI was analyzed using the multivariate Cox proportional-hazards regression model, which included all the predictive factors with a P value <0.05 from the univariate analyses. The statistical analyses were performed using SPSS software for Mac (version 26.0; SPSS Inc., Chicago, IL, USA). All the tests were two-sided, and the results were considered statistically significant when the P value was <0.05.

Results

Patient characteristics and pathological variables

The patient characteristics and pathological variables of the 371 patients are summarized in *Table 1*. The cohort of patients comprised 229 men (61.7%) and 142 women (38.3%), with a median age of 60 (range, 20–83) years at the time of the curative-intent resection. Among the patients, 88 (23.7%), 113 (30.5%), and 170 (45.8%) of the tumors occurred in the right colon, left colon, and rectum, respectively. Using the American Joint Committee on Cancer TNM staging system, 299 (80.6%) patients were classified as pT3, and 72 (19.4%) were classified as pT4. The median tumor size was 4.5 (range, 1.6–14) cm, and PNI was observed in 82 (22.1%) patients. After surgery, 157 (42.3%) patients received adjuvant chemotherapy, and 45 (12.1%) suffered from postoperative morbidity.

Clinicopathological variables associated with the incidence of PNI among stage II CRC patients

The comparison results for the patients according to their PNI status are set out in *Table 2*. The incidence of PNI was significantly correlated with preoperative serum CEA levels (P=0.030), gross tumor type (P=0.010), tumor differentiation (P=0.010), p stage (P<0.001), and EMVI (P<0.001). A high CEA level, an ulcerative type of lesion, poor differentiation, T4 stage, and EMVI-negative patients were more frequently identified as PNI (+). Additionally, the incidence of PNI was not associated with age, sex, family history, tumor location, tumor size, or MSI status. After surgery, the PNI (+) patients were more likely to accept adjuvant chemotherapy than PNI-negative (–) patients (P=0.008).

Significance of PNI as a predictor among patients with stage II CRC

The prognostic significance of PNI and the other clinicopathological variables was examined using univariate regression models (see *Table 3*). PNI and preoperative serum CEA levels were the only two factors that were associated with both OS and DFS. Conversely, age, sex, family history,

Table 1 Clinical histopathological characteristics of PNI stage II CRC patients who underwent curative-intent surgery at the National Cancer Center/Cancer Hospital in 2014

Characteristics	Total (n=371)
Age at operation (years), median, range	60, 20–83
<60, n (%)	179 (48.2)
≥60, n (%)	192 (51.8)
Gender, n (%)	
Male	229 (61.7)
Female	142 (38.3)
Family history, n (%)	
Yes	61 (83.6)
No	310 (16.4)
Preoperative CEA level (ng/mL), median, range	2.965, 0.47–342.4
Location of the tumor, n (%)	
Right-sided colon	88 (23.7)
Left-sided colon	113 (30.5)
Rectum	170 (45.8)
Maximal diameter of the tumor (cm), median, range	4.5, 1.6–14
<4.5, n (%)	160 (43.1)
≥4.5, n (%)	211 (56.9)
Gross type, n (%)	
Protruded	177 (47.7)
Ulcerative	193 (52.0)
Unknown	1 (0.3)
Tumor differentiation, n (%)	
Poor/mucinous	95 (25.6)
Good/moderate	276 (74.4)
Tumor p stage, n (%)	
T3	299 (80.6)
T4a	66 (17.8)
T4b	6 (1.6)
PNI, n (%)	
Yes	82 (22.1)
No	289 (77.9)
EMVI, n (%)	
Yes	42 (11.3)
No	321 (86.5)
Unknow	8 (2.2)
MSI, n (%)	
Positive	39 (10.5)
Negative	332 (89.5)
Postoperative chemotherapy, n (%)	
Yes	157 (42.3)
No	210 (56.6)
Unknow	4 (1.1)
Postoperative morbidity, n (%)	
Yes	45 (12.1)
No	326 (87.9)

PNI, perineural invasion; CRC, colorectal cancer; CEA, carcinoembryonic antigen; EMVI, extramural vascular invasion; MSI, microsatellite instability.

tumor location, tumor size, differentiation, EMVI and MSI status, and postoperative chemotherapy did not affect patient outcomes.

With a median follow-up period of 71 (range, 2–86) months, the 5-year OS rate of this cohort was 94.5%, and the 5-year DFS rate was 87.9%. In all patients, PNI affected OS [84.1% *vs.* 96.5% for PNI (+) and PNI (–) patients, respectively, P<0.001; *Figure 1A*]. Notably, when the patients were divided according to tumor location (right-sided colon, left-sided colon, and rectum), their OS rates (P=0.011, P=0.866, and P<0.001, respectively; *Figure 1B-1D*) were differentially affected by PNI. DFS was the same as OS, PNI affected DFS [75.6% *vs.* 91.3% for PNI (+) and PNI (–), respectively, P<0.001; *Figure 2A*], and for right-sided colon, left-sided colon, and rectum their DFS were also differently affected (P=0.005, P=0.613, and P<0.001, respectively; *Figure 2B-2D*). In brief, while the occurrence of PNI was not associated with the location of the tumor, the presence of PNI was correlated with the prognosis of CRC at different sites. PNI (+) right-sided colon cancer and rectal cancer patients had lower OS and DFS than PNI (–)

Table 2 Comparison of patients according to whether PNI was positive or not

Characteristics	PNI (+) (n=82)		PNI (–) (n=289)		P value
	N	%	N	%	
Age at operation (years), median, range	61, 21–78		60, 20–83	25.6	0.695
<60	38	46.3	141	48.8	
≥60	44	53.7	148	51.2	
Gender					0.874
Male	50	61	179	61.9	
Female	32	39	110	38.1	
Family history					0.861
Yes	14	17.1	47	16.3	
No	68	82.9	242	83.7	
Preoperative CEA level (ng/mL), median, range	4.37, 0.72–342.4		2.77, 0.47–228.2		0.030
Location of the tumor					0.655
Right-sided colon	17	20.7	71	24.6	
Left-sided colon	24	29.3	89	30.8	
Rectum	41	50	129	44.6	
Maximal diameter of the tumor (cm), median, range	4.5, 2.2–10.5		4.5, 1.6–8.4		0.872
<4.5	36	43.9	124	42.9	
≥4.5	46	56.1	165	57.1	
Gross type					0.010
Protruded	29	35.4	148	51.4	
Ulcerative	53	64.6	140	48.6	
Tumor differentiation					0.010
Poor/mucinous	30	36.6	65	22.5	
Good/moderate	52	63.4	224	77.5	
Tumor p stage					<0.001
T3	52	63.4	247	85.5	
T4a	28	34.1	38	13.1	
T4b	2	2.4	4	1.4	
EMVI					<0.001
Yes	55	73.3	266	92.4	
No	20	26.7	22	7.6	
MSI					0.509
Positive	7	8.5	32	11.1	
Negative	75	91.5	257	88.9	
Postoperative morbidity					<0.001
Yes	20	24.4	25	8.7	
No	62	75.6	264	91.3	
Postoperative chemotherapy					0.008
Yes	45	55.6	112	39.2	
No	36	44.4	174	60.8	

PNI, perineural invasion; PNI (+), PNI-positive; PNI (–), PNI-negative; CEA, carcinoembryonic antigen; EMVI, extramural vascular invasion; MSI, microsatellite instability;

Table 3 Univariate Cox-regression analyses of potential prognostic factors for OS and DFS in stage II CRC patients who underwent curative-intent surgery

Variables	Univariate analysis			
	OS		DFS	
	HR (95% CI)	P	HR (95% CI)	P
Age, years	1.022 (0.986–1.058)	0.232	1.020 (0.995–1.047)	0.123
Gender	0.957 (0.440–2.083)	0.912	0.706 (0.391–1.274)	0.248
Family history	0.867 (0.300–2.511)	0.793	1.173 (0.589–2.338)	0.650
Preoperative CEA level, ng/mL	1.012 (1.004–1.019)	0.002	1.009 (1.002–1.015)	0.007
Location of the tumor	1.136 (0.712–1.181)	0.593	1.427 (0.992–2.051)	0.055
Maximal diameter of the tumor, cm	0.969 (0.774–1.212)	0.780	0.859 (0.715–1.032)	0.105
Gross type	1.613 (0.744–3.498)	0.226	1.275 (0.739–2.200)	0.383
Tumor differentiation	0.848 (0.373–1.928)	0.693	0.849 (0.467–1.544)	0.592
Tumor p stage	1.286 (0.605–2.734)	0.513	1.017 (0.561–1.844)	0.956
PNI	4.902 (2.291–10.491)	<0.001	3.075 (1.785–5.298)	<0.001
EMVI	1.097 (0.328–3.668)	0.880	1.926 (0.934–3.971)	0.076
MSI	0.235 (0.031–1.760)	0.159	0.416 (0.128–1.352)	0.145
Postoperative therapy	0.782 (0.358–1.708)	0.537	1.073 (0.621–1.855)	0.801

OS, overall survival; DFS, disease-free survival; CRC, colorectal cancer; HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; PNI, perineural invasion; EMVI, extramural vascular invasion; MSI, microsatellite instability.

patients; however, no such differences were observed in the left-sided colon cancer patients.

PNI is an independent prognostic factor for outcomes among stage II CRC patients

According to the univariate regression models, PNI and preoperative serum CEA levels were correlated with OS and DFS. The multivariate analysis also revealed that both PNI and preoperative serum CEA levels were independent prognostic factors of DFS (see *Table 4*).

Clinicopathological variables associated with outcomes of PNI (+) stage II CRC patients

According to the univariate regression models (see *Table 5*), preoperative serum CEA levels were the only factor correlated with OS and DFS in PNI (+) stage II CRC patients.

Effects of adjuvant chemotherapy on PNI in patients with stage II CRC

Given the importance of PNI, we analyzed whether postoperative adjuvant chemotherapy improved outcomes in the PNI (+) group. The results showed that postoperative adjuvant chemotherapy did not improve OS (P=0.077 and P=0.940, respectively; *Figure 3A*,*3B*) or DFS (P=0.267 and P=0.480, respectively; *Figure 3C*,*3D*) in either PNI (–) or PNI (+) CRC patients.

Discussion

The most widely accepted definition of PNI is tumor cells within any layer of the nerve sheath or tumor cells in the perineural space that involves at least 1/3 of the nerve circumference (9). The clinical significance of PNI was first described in head and neck carcinomas and was considered to be a risk factor for intracranial extension (10). More recently, PNI has also been identified as a key pathological feature of other solid tumors, including pancreatic cancer (11), prostate cancer (12), biliary tract cancer (13) and gastric cancer (14). Additionally, many studies have shown the significance of PNI in CRC (15,16).

A number of hypotheses have been put forward as to the route for CRC metastasis through PNI. For example, it has been hypothesized that cancer cells within the nerve spread

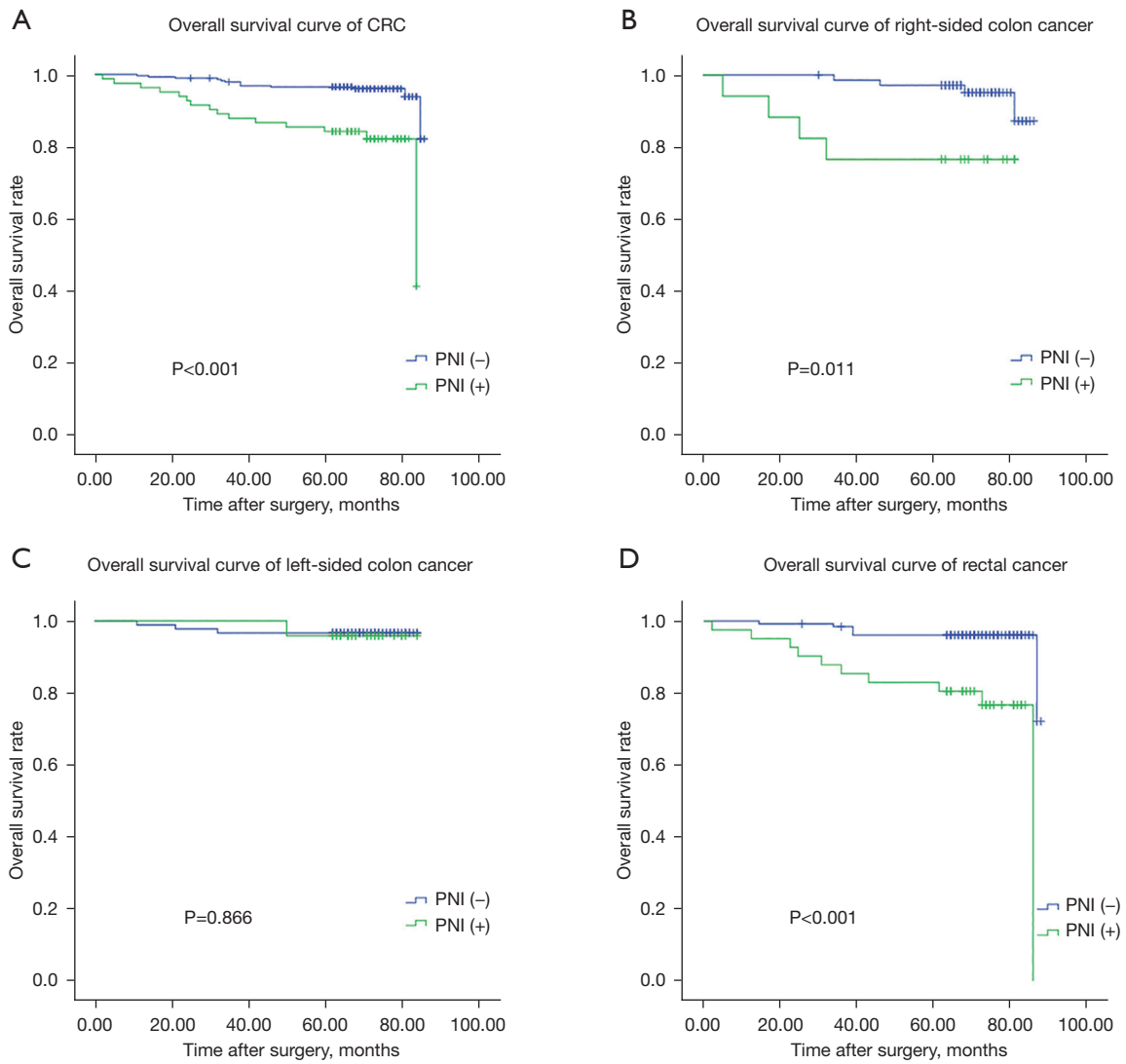

Figure 1 Kaplan-Meier analysis of OS in stage II CRC patients according to tumor sites: (A) CRC as a whole, (B) right-sided colon cancer, (C) left-sided colon cancer; and (D) rectal cancer. CRC, colorectal cancer; PNI, perineural invasion; PNI (+), PNI-positive; PNI (–), PNI-negative; OS, overall survival.

to the celiac ganglia along the superior mesenteric and then to the liver because of the shared preganglionic origin of the sympathetic nerves that innervate the liver and colorectum (17,18). Conversely, others have hypothesized that PNI is an invasion rather than a simple tumor diffusion: PNI induces changes in the perineural microenvironment, alters neurotrophic factors and chemokines, and enhances the ability of tumor cell invasion, inducing cancer aggressiveness and metastasis (19).

In our study, PNI was observed in 22.1% of the patients who underwent surgery for stage II CRC. This PNI prevalence conformed with a systematic review that found a weighted average detection rate for PNI of 17% (range, 8–42%) (7). A previous study revealed that the presence of PNI was a significant independent prognostic factor of DFS in multivariate analyses of stage I–II colon cancer patients treated with curative surgery (20). Regarding rectal cancer, Kinugasa *et al.* reported that PNI was a significant prognostic factor and that PNI status should be considered for therapy stratification (17). Consistent with previous studies, our study showed that PNI is an independent prognostic factor for outcomes among stage II CRC

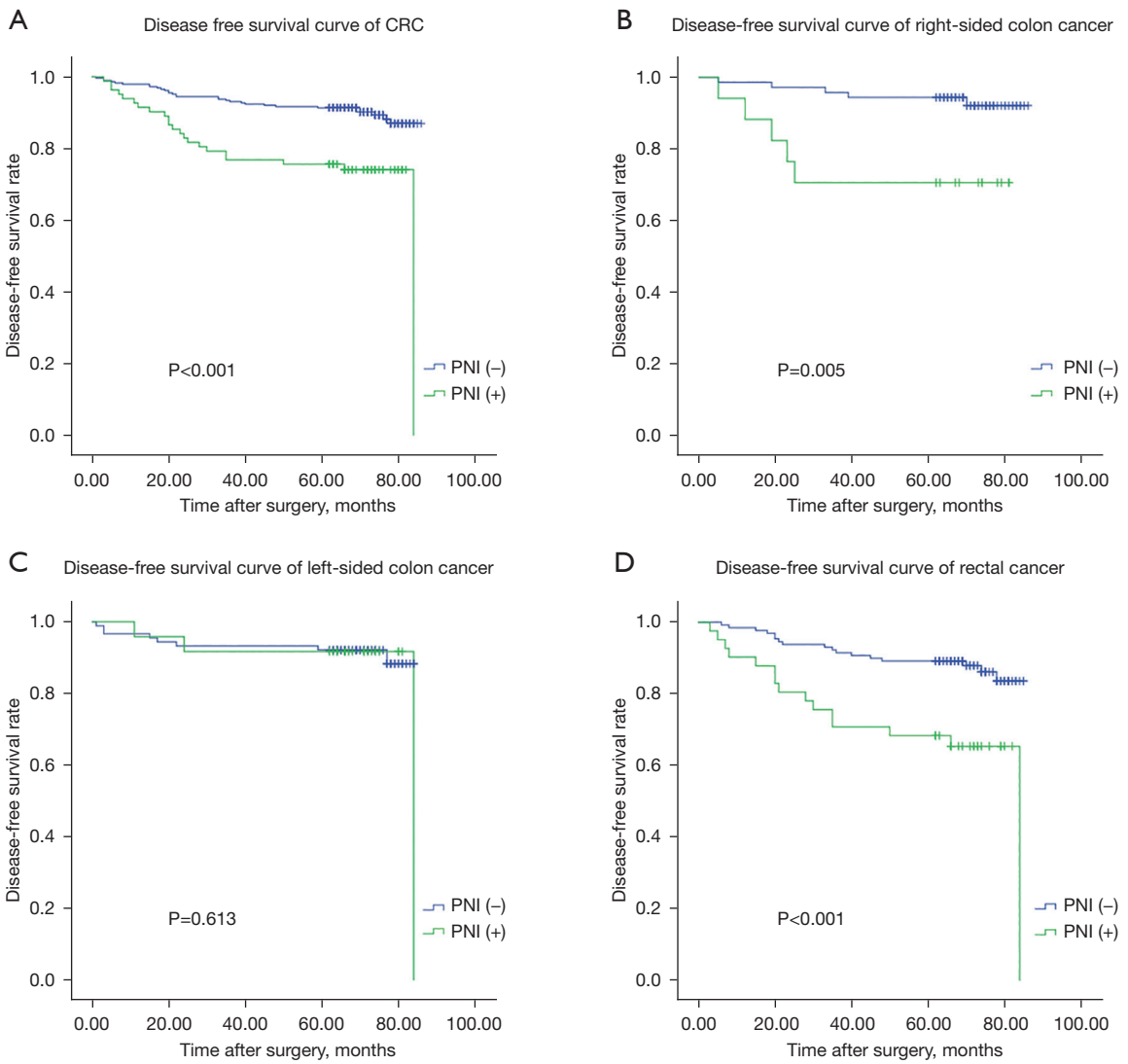

Figure 2 Kaplan-Meier analysis of DFS in stage II CRC patients according to tumor sites: (A) CRC as a whole, (B) right-sided colon cancer, (C) left-sided colon cancer, and (D) rectal cancer. CRC, colorectal cancer; PNI, perineural invasion; PNI (+), PNI-positive; PNI (–), PNI-negative; DFS, disease-free survival.

Table 4 Multivariate Cox-regression analysis of OS and DFS in stage II CRC patients

Variables	Multivariate analysis			
	OS		DFS	
	HR (95% CI)	P	HR (95% CI)	P
Preoperative CEA level, ng/mL	1.011 (1.004–1.019)	0.002	1.009 (1.002–1.015)	0.006
PNI	3.966 (1.642–9.575)	0.002	2.950 (1.546–5.626)	0.001

OS, overall survival; DFS, disease-free survival; CRC, colorectal cancer; HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; PNI, perineural invasion.

Table 5 Univariate Cox-regression analysis of OS and DFS in PNI (+) stage II CRC patients

Variables	Univariate analysis			
	OS		DFS	
	HR (95% CI)	P	HR (95% CI)	P
Age, years	1.011 (0.961–1.064)	0.665	1.025 (0.983–1.068)	0.245
Gender	0.853 (0.286–2.546)	0.775	0.930 (0.385–2.243)	0.871
Family history	0.642 (0.140–2.511)	0.567	0.761 (0.252–2.293)	0.627
Preoperative CEA level, ng/mL	1.012 (1.004–1.020)	0.005	1.012 (1.004–1.020)	0.004
Location of the tumor	1.167 (0.582–2.341)	0.664	1.269 (0.714–2.258)	0.417
Maximal diameter of the tumor, cm	1.040 (0.743–1.456)	0.819	0.936 (0.703–1.245)	0.648
Gross type	0.605 (0.219–1.676)	0.334	0.615 (0.270–1.399)	0.246
Tumor differentiation	1.407 (0.441–4.487)	0.564	1.976 (0.724–5.394)	0.184
Tumor p stage	0.713 (0.278–1.828)	0.481	1.359 (0.701–2.633)	0.363
EMVI	0.518 (0.116–2.317)	0.390	1.008 (0.369–2.754)	0.987
MSI	0.500 (0.060–4.151)	0.521	0.267 (0.034–2.114)	0.211
Postoperative therapy	1.042 (0.361–3.004)	0.940	1.371 (0.568–3.308)	0.483

OS, overall survival; DFS, disease-free survival; PNI, perineural invasion; PNI (+), PNI-positive; CRC, colorectal cancer; HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; EMVI, extramural vascular invasion; MSI, microsatellite instability.

patients in univariate and multivariate analyses (21,22). To better understand the clinicopathological factors associated with PNI, we first found that the incidence of PNI in stage II CRC patients was significantly correlated with preoperative serum CEA levels, gross tumor type, tumor differentiation, p stage, and EMVI.

Both OS and DFS were impaired by PNI. Notably, we first found that while the occurrence of PNI was not associated with the location of the tumor, the presence of PNI was correlated with the prognosis of CRC in different sites. This result may have been caused by the clinical and molecular heterogeneity of different tumor sites. In the current era of personalized medicine, carcinomas of the right colon, left colon, and rectum are regarded as different tumor entities. From the perspective of the embryonic origin, right-sided colon cancer derives from the embryonic midgut, while left-sided colon cancer and rectal cancer derive from the embryonic hindgut (23). The rectum embryonically belongs to the hindgut; however, rectal cancer differs from colon cancer in its metastatic patterns and therapy-related factors (24,25) and thus is often described separately (26). The splenic flexure is often used to differentiate between the left and right sides of the colon in clinical retrospective report (27). From the perspective of anatomy and blood supply, the superior mesenteric artery supplies the proximal colon, while the inferior mesentery artery supplies the distal colon and rectum because of the different embryological origins (28). From a molecular point of view, right-sided colon cancers have higher rates of MSI and higher v-raf murine sarcoma viral oncogene homolog B1, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, and transforming growth factor, beta receptor II mutation rates (29), while left-sided colon cancer is more associated with mutations in the *adenomatous polyposis coli*, *Kirsten-ras*, *SMAD4*, and *TP53* genes (30). Rectal cancers have higher rates of *TOPO1* expression and *Her2/neu* amplification (31). Additionally, gut microbiota dysbiosis is involved in the progression of CRC (32), and different sites of the colorectum have different microbiota phenotypes (33).

As to the significance of PNI, we further analyzed the clinicopathological variables associated with outcomes of PNI (+) stage II CRC patients. However, only preoperative serum CEA levels were a positive indicator for further treatment. Thus, elevated CEA levels can guide the selection of patients for further treatment.

Several studies have suggested that PNI status can be used to select patients with stage I–II CRC for adjuvant

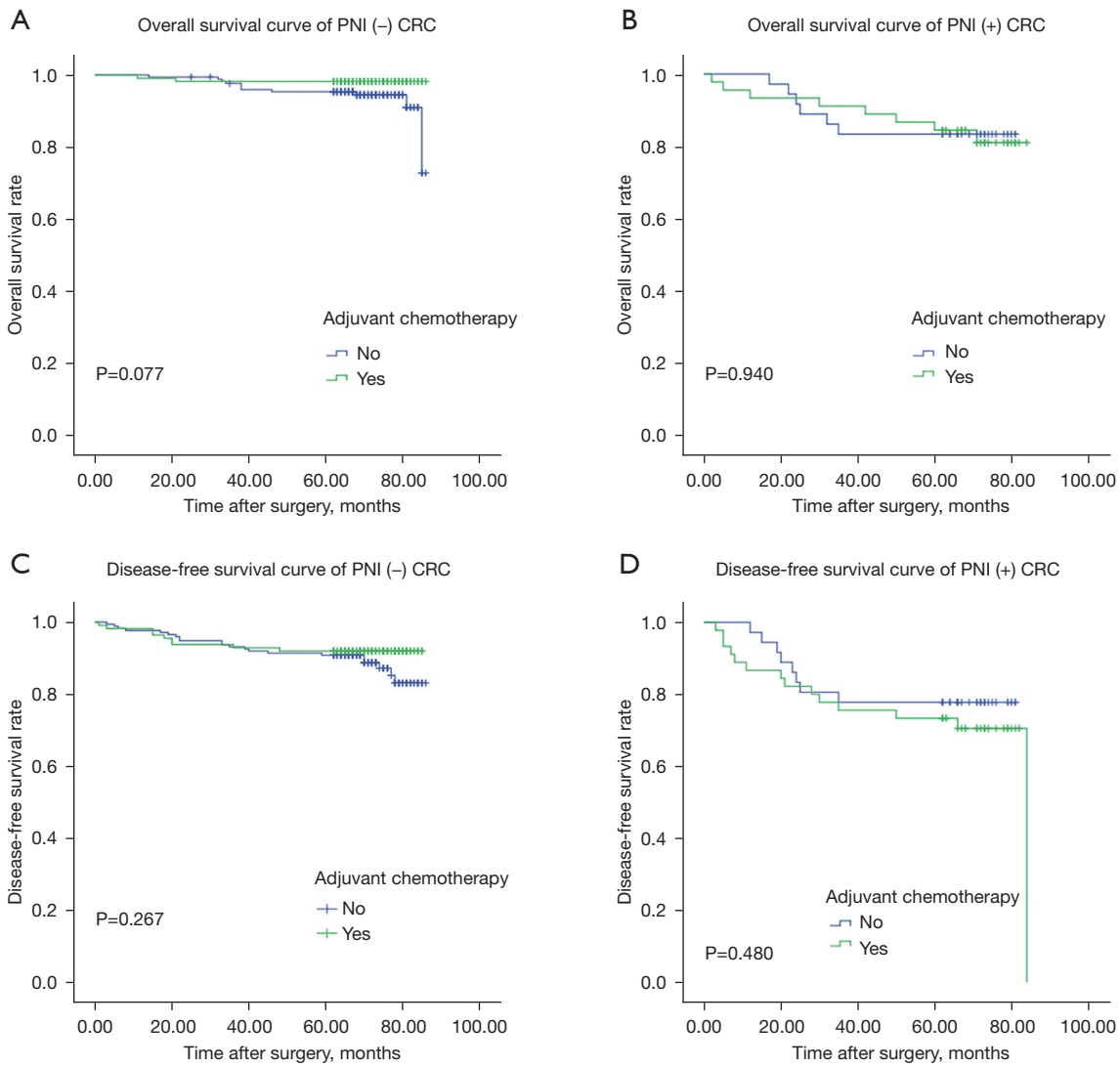

Figure 3 Kaplan-Meier analysis of OS and DFS in stage II CRC patients according to postoperative adjuvant chemotherapy status and PNI status. (A) OS of PNI (–) patients, (B) OS of PNI (+) patients, (C) DFS of PNI (–) patients, (D) DFS of PNI (+) patients. PNI, perineural invasion; PNI (–), PNI-negative; CRC, colorectal cancer; PNI (+), PNI-positive; OS, overall survival; DFS, disease-free survival.

chemotherapy (20,34). Fluorouracil-based adjuvant chemotherapy was shown to reverse the adverse effect of PNI on 5- to 10-year DFS (20). This study failed to find that postoperative adjuvant chemotherapy improved the OS and DFS of stage II CRC patients. However, given the significance of PNI, therapies specifically effective for PNI need to be further explored.

Our study has several limitations. First, it was a single-center and retrospective study and had a small sample size. Second, patients had difficulties recalling their chemotherapy regimens and durations during follow up.

Conclusions

In the present study, we found that PNI is an independent prognostic factor in stage II CRC patients, and the incidence of PNI is significantly correlated with preoperative serum CEA levels, gross tumor type, tumor differentiation, p stage, and EMVI. PNI was an independent poor predictor for DFS and OS. Among the PNI (+) patients, preoperative serum CEA levels were positively correlated with DFS and OS. Traditional postoperative adjuvant chemotherapy did not improve the outcomes of PNI (+) stage II patients.

However, given the importance of PNI, further research should be conducted on PNI.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College approved this study (approval number: 21/13902810). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was taken from all the patients.

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