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RESEARCH PAPER

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Impact of perineural invasion on survival in node negative colon cancer

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ABSTRACT

Perineural invasion (PNI) has been implicated as a poor prognostic indicator in many cancers. The National Comprehensive Cancer Network recommends consideration of observation or adjuvant therapy in the presence of PNI in early colon cancer. These recommendations are based on single institutional studies that fail to evaluate PNI within the context of adjuvant chemotherapy. The US National Cancer Database (2004–2012) was reviewed for patients with node negative colon cancer, and stratified by PNI and receipt of chemotherapy.

Of 21,488 patients evaluated, 55.2% had T3 disease (n = 11,852), 23.1% had T2 (n = 4,971), 14.4% had T1 (n = 3,088), and 7.3% had T4 disease (n = 1,577); 4.6% (n = 987) had PNI. Most patients (86.8%, n = 18,641) did not have PNI and did not receive chemotherapy; 8.7% (n = 1,860) did not have PNI but received chemotherapy; 3.7% (n = 785) had PNI and did not receive chemotherapy, and 0.9% (n = 202) had PNI and received chemotherapy. Among those with PNI, patients who received chemotherapy tended to be younger ($P<0.001$), covered by private insurance ($P<0.001$), with fewer comorbidities ($P<0.001$), and greater T stage disease ($P<0.001$). Those with PNI who received chemotherapy had significantly improved survival over those who did not in T3–4 disease ($P<0.001$), but not in T1–2 disease. On multivariate analysis, those with PNI had a 38% greater hazard of mortality (HR 1.38, $P<0.001$). Additionally, chemotherapy decreased the hazard of mortality by 43% (HR 0.57, $P<0.001$). PNI appears to be an independent poor prognostic indicator in stage T3–4 node negative colon cancer. Chemotherapy administered to this patient population is associated with improved survival.

Abbreviations: AJCC, American Joint Committee on Cancer; CCI, Charlson/Deyo comorbidity index; NCCN, National Comprehensive Cancer Network; NCDB, National Cancer Data Base; PNI, Perineural invasion

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Introduction

The role of adjuvant chemotherapy in node positive colon cancer has been established through several randomized trails.[1-7] These studies show a 22–32 percent risk reduction in mortality in stage III patients who undergo surgical resection and adjuvant chemotherapy.[1-4,5,8] However, the role of chemotherapy in stage II node negative disease remains unclear.[6,7,9] Other clinicopathologic features associated with worse prognosis in early stage disease include lymphovascular invasion, bowel obstruction and perforation.[10-14] There is conflicting evidence supporting the benefit of adjuvant chemotherapy in these higher-risk subpopulations.[2,15-18] Perineural invasion (PNI) has been implicated as a poor prognostic indicator in many cancers, including colon and rectal cancer.[19-23] The 5-year overall survival rate has been reported as 72% for PNI-negative tumors versus 25% for PNI-positive tumors.[21]

To date, guidelines from the National Comprehensive Cancer Network (NCCN) recommend consideration of adjuvant chemotherapy, participation in a clinical trial, or observation in the presence of PNI in early colon cancer.[24] These recommendations are based on evidence that PNI is an independent adverse prognostic factor.[11,21,22] The majority of existing evidence comes from single institutional studies that fail to evaluate PNI within the context of adjuvant chemotherapy. The objective of this study was to evaluate the impact of PNI on survival in node negative colon cancer in a large Western population.

Results

This study population consisted of 7,960 (37.0%) patients with stage I disease (overall 5-year survival: 69.9%), and 13,528 (63.0%) patients with stage II disease (overall 5-year survival: 58.1%), 51.8% females, with a median age of 72 y (Fig. 1). Of the 21,488 patients evaluated, the majority had T3 disease (n = 11,852, 55.2%), 23.1% had T2 disease (n = 4,971), 14.4% had T1 (n = 3,088), and 7.3% had

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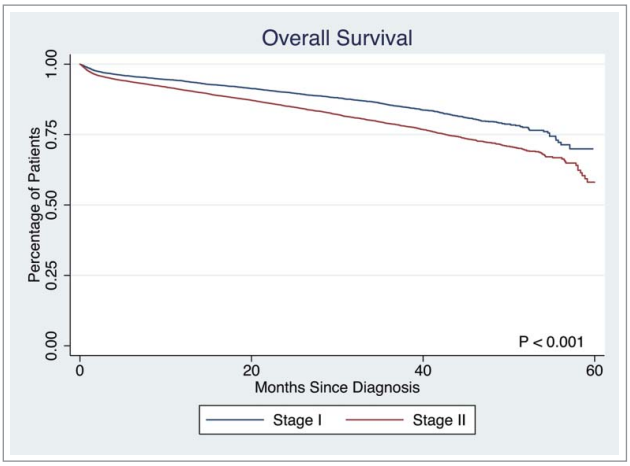

Figure 1. Overall survival in Stage I and Stage II disease.

T4 disease (n = 1,577); 4.6% (n = 987) had PNI. The majority of the study population did not have PNI and did not receive chemotherapy (86.8%, n = 18,641); 8.7% (n = 1,860) did not have PNI but received chemotherapy; 3.7% (n = 785) had PNI and did not receive chemotherapy, and 0.9% (n = 202) had PNI and received chemotherapy.

Patient, disease and treatment characteristics, stratified by presence of PNI and receipt of chemotherapy, are displayed in Table 1. Patients with PNI who received chemotherapy tended to be younger ($p < 0.0001$), covered by private insurance ($p < 0.0001$), with fewer comorbidities ($p < 0.0001$). They tended to have more advanced T stage ($p < 0.0001$), and pathological stage disease. There was no difference in type of surgery received ($p = 0.939$) or number of lymph nodes resected ($p = 0.084$). Patients without PNI who received chemotherapy also tended to be younger ($p < 0.0001$), covered by private insurance ($p < 0.0001$), with fewer comorbidities ($p < 0.0001$). They too, had more advanced T stage ($p < 0.0001$), and pathological stage disease ($p < 0.0001$), and greater number of lymph nodes resected ($p < 0.0001$).

The presence of PNI was not associated with a difference in survival in T1 or T2 stage disease ($p = 0.7839$, $p = 0.1379$, respectively). However, PNI was associated with significantly lower survival rate in T3 and T4 stage disease (5-year survival: 53.7% vs. 58.3%, $p < 0.0001$, 45.9% vs. 57.6%, $p = 0.0033$, respectively). Overall survival in T3 disease is depicted in Fig. 2. Patients with PNI who did not receive chemotherapy had significantly worse survival than those without PNI who did not receive chemotherapy, those with PNI who received chemotherapy, and those without PNI who received chemotherapy (5-year survival: 49.1%, 54.1%, 81.1%, and 83.8%, respectively, $p < 0.001$). A similar statistically significant survival pattern was observed in T4 disease (5-year survival: 21.9%, 53.1%, 74.0%, and 69.9%, respectively, $p < 0.001$) (Fig. 3).

Results of a multivariable Cox proportional hazards model, controlling for patient, disease, and treatment characteristics are reported in Table 2. The presence of PNI was associated with a 41% greater hazard of mortality (HR 1.41, $p < 0.001$). Receipt of adjuvant chemotherapy was associated with a 44% reduction in the hazard of mortality (HR 0.56, $p < 0.001$).

Discussion

The results of this study suggest the poor prognostic implications of PNI, and the survival benefits adjuvant chemotherapy offers in stage T3 and T4 node negative colon cancer.

Multiple single institutional studies suggest the presence of PNI is a poor prognostic indicator.[19-23] The current large, national, study found patients with PNI had a 38% greater hazard of mortality ($p < 0.001$). A much smaller retrospective study of 2,649 patients from the Swedish Colon Cancer Registry with TNM stage II disease reported increased risk of recurrence in patients with PNI.[19] Huh et al. reported a retrospective study of 1,437 patients who underwent surgery for stage II or III colon cancer reported that the presence of both lymphovascular and PNI was an independent poor prognostic factor for both overall and disease-free survival.[20] Liebig at al. evaluated 269 patients with resected colon cancer and identified PNI as an independent prognostic factor for both cancer-specific overall survival and disease-free survival.[21] None of these prior reports addressed the impact of adjuvant chemotherapy in patients with PNI.

Currently, the NCCN guideline recommends observation, enrollment in a clinical trial or adjuvant chemotherapy in the setting of PNI.[24] The results of this study advocate for the administration of adjuvant chemotherapy for patients with T3 or T4 disease and PNI. A single institutional study by Suzuki et al. retrospectively reviewed 178 patients with stage I-III colon cancer who underwent curative surgery from 1999–2004, and reported PNI as a strong prognostic factor, with adjuvant chemotherapy attenuating the effects.[25] Another small study of 509 patients who underwent curative surgery for pT3 or pT4 colon cancer from 1997 to 2001 reported significantly worse survival in patients with PNI as compared with patients without PNI, irrespective of adjuvant chemotherapy use.[22] In this study, patients with PNI who received chemotherapy, had better survival compared with patients without PNI who did not receive chemotherapy. This likely reflects in part a selection bias due to the retrospective nature of the study, and highlights advancements in chemotherapy between the 2 studies.

To our knowledge, this represents the largest and most contemporary analysis of PNI in colon cancer. However, there are some important limitations which should be acknowledged. The NCDB is a large data set incorporating multiple institutions with the potential for coding inconsistencies and errors. As shown in Table 1, the cohorts who received chemotherapy differed in patient and disease demographics, illustrating a selective bias inherent to the retrospective nature of this study. However, multivariate analysis controlling for these factors was performed. Postoperative occurrences that may have influenced the treatment course were not captured in this study. Furthermore, the chemotherapy regimen and duration used was not captured by this data set, and thus

Table 1. Patient, disease and surgery demographics.

	Neural invasion			No neural invasion			
	Chemotherapy (n = 202)	None (n = 785)	p-value	Chemotherapy (n = 1,860)	None (n = 18,641)	p-value	p-value
Age	60.4	72.2	<0.0001	60.7	71.2	<0.0001	<0.0001
18–59	46.0%	17.8%		44.7%	18.5%		
60–69	31.2%	19.9%		30.3%	22.3%		
70–79	18.3%	27.3%		20.3%	29.7%		
80–90	4.5%	35.0%		4.8%	29.4%		
Sex			0.400			0.027	0.043
Male	48.0%	51.3%		50.5%	47.8%		
Female	52.0%	48.7%		49.5%	52.2%		
Race			0.455			<0.0001	<0.0001
White (non-Hispanic)	70.3%	75.4%		70.5%	77.2%		
Black (non-Hispanic)	15.3%	11.7%		13.4%	10.5%		
Other (non-Hispanic)	3.5%	3.4%		3.7%	3.0%		
Hispanic	10.9%	9.4%		12.4%	9.3%		
Insurance			<0.0001			<0.0001	<0.0001
Private	48.0%	23.3%		45.4%	27.2%		
Medicare	36.6%	67.0%		38.0%	64.9%		
Medicaid and other government	6.9%	3.7%		8.4%	3.8%		
Unknown	0.5%	1.9%		1.2%	1.3%		
Not ensured	7.9%	4.1%		7.0%	2.7%		
Median income			0.269			0.05	0.166
<58,000	16.3%	19.9%		20.4%	18.0%		
58,000 -74,000	21.3%	25.4%		25.6%	25.2%		
74,000 - 93,000	30.7%	26.0%		25.3%	26.6%		
>93,000	30.7%	27.8%		28.3%	29.6%		
Comorbidities			<0.0001			<0.0001	<0.0001
CCI score 0	78.7%	64.6%		75.6%	65.3%		
CCI score 1	15.8%	23.3%		19.6%	24.7%		
CCI score 2	5.4%	12.1%		4.8%	10.0%		
Facility type			0.026			0.068	0.001
Community	14.4%	13.9%		15.8%	16.2%		
Comprehensive community	42.1%	50.3%		50.2%	53.1%		
Academic/research	27.7%	29.0%		24.6%	24.0%		
Other	0.0%	0.1%		0.3%	0.2%		
Facility location			0.236			0.001	0.001
Northeast	19.3%	22.4%		18.6%	18.6%		
South	44.1%	38.6%		40.3%	40.2%		
Midwest	21.8%	24.1%		24.7%	25.1%		
West	8.9%	13.4%		12.2%	15.0%		
TNM: T			<0.0001			<0.0001	<0.0001
T1	0.0%	4.6%		0.8%	16.3%		
T2	1.0%	11.2%		2.9%	25.9%		
T3	59.4%	69.9%		68.5%	53.2%		
T4	39.6%	14.3%		27.8%	4.7%		
Surgery type			0.998			0.001	<0.0001
Partial or hemicolectomy	95.5%	95.5%		94.1%	95.8%		
Total colectomy	4.5%	4.5%		5.9%	4.2%		
Number of regional lymph nodes removed	19.9	19.0	0.285	20.8	19.2	<0.0001	0.007
Pathological stage			<0.0001			<0.0001	<0.0001
Stage 1	0.5%	15.5%		3.4%	41.7%		
Stage 2	99.5%	84.5%		96.6%	58.3%		

outcomes specific to particular adjuvant regimens cannot be extrapolated.

Methods

Data

The National Cancer Data Base (NCDB) is a clinical oncology database, sourced from hospital registry data collected from over 1,500 Commission on Cancer accredited facilities across the United States. The NCDB captures approximately 80% of cancer cases in the United States from 1998 to 2012. This was a retrospective cohort study of clinical data from this registry from 2004–2012. The Penn State Health Institutional Review Board reviewed and approved the study.

Patient selection

The NCDB was reviewed for patients diagnosed with node-negative colon cancer. Patients with unknown nodal status were excluded. This analysis included pathological stage I and II adenocarcinoma of the large intestine, identified using

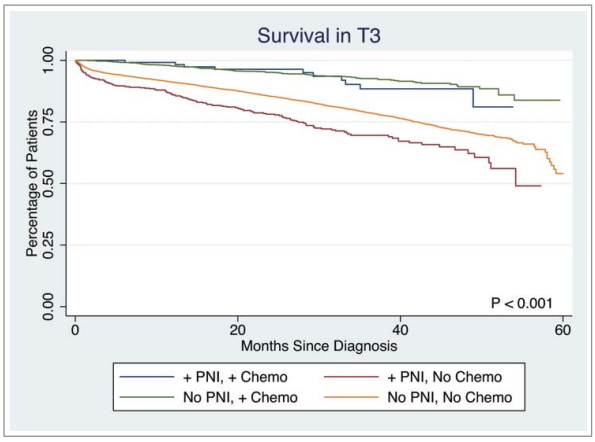

Figure 2. Survival in Stage T3 disease.

histology ICD-O-3 code 8140/3. Patients with positive surgical margins, those who received neoadjuvant therapy, and those who underwent local excision or unspecified surgical procedures were also excluded.

Outcomes and covariates

The primary outcome assessed was survival in days from date of diagnosis. The presence of PNI as documented in pathology reports was coded within the database. Univariate analyses compared demographic data including age, sex, race, insurance type (private, Medicare, Medicaid and other government programs, unknown, not ensured), median income and the Charlson/Deyo comorbidity index (CCI), an index of 15 comorbidities including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, moderate or severe liver disease and AIDS.[26,27]

Treatment facilities were stratified by facility type (community, comprehensive community, academic or research institution, other), and geographic region (Northeast, South, Midwest, West). Disease was characterized by the American

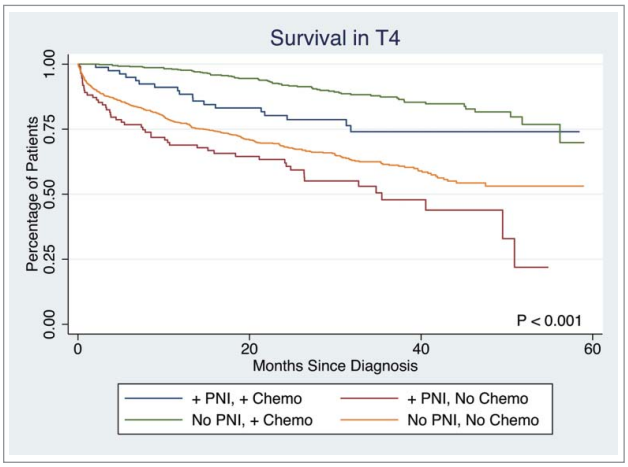

Figure 3. Survival in Stage T4 disease.

Table 2. Multivariate survival analysis.

	95% Confidence interval			
	Hazard ratio	*lower*	*upper*	p-value
Perineural invasion				
None	Reference			
Present	1.38	1.20	1.57	<0.001
Age				
18–59	Reference			
60–69	1.38	1.20	1.57	<0.001
70–79	1.68	1.44	1.98	<0.001
80–90	2.72	2.32	3.19	<0.001
Sex				
Male	Reference			
Female	0.78	0.73	0.84	<0.001
Race				
White (non-Hispanic)	Reference			
Black (non-Hispanic)	1.03	0.92	1.16	0.575
Other (non-Hispanic)	1.02	0.81	1.27	0.893
Hispanic	1.01	0.90	1.14	0.848
Insurance				
Private	Reference			
Medicare	1.27	1.14	1.41	<0.001
Medicaid and other government	1.56	1.28	1.91	<0.001
Unknown	1.37	1.01	1.87	0.043
Not ensured	1.39	1.07	1.80	0.013
Median income				
<58,000	Reference			
58,000 -74,000	1.02	0.92	1.12	0.766
74,000 - 93,000	0.94	0.85	1.04	0.241
>93,000	0.87	0.78	0.96	0.006
Comorbidities				
CCI score 0	Reference			
CCI score 1	1.34	1.24	1.44	<0.001
CCI score 2	2.11	1.93	2.31	<0.001
Facility type				
Community	Reference			
Comprehensive community	1.00	0.92	1.09	1.000
Academic/research	0.94	0.85	1.03	0.188
Other	0.97	0.50	1.87	0.917
Facility location				
Northeast	Reference			
South	0.99	0.90	1.09	0.873
Midwest	0.98	0.89	1.08	0.661
West	0.99	0.88	1.11	0.884
Surgery type				
Partial or hemicolectomy	Reference			
Total colectomy	1.44	1.25	1.67	<0.001
TNM: T				
T1	Reference			
T2	1.15	1.01	1.31	0.031
T3	1.49	1.32	1.67	<0.001
T4	2.91	2.51	3.37	<0.001
Adjuvant therapy				
None	Reference			
Chemotherapy	0.57	0.48	0.67	<0.001
Radiation	1.22	0.58	2.56	0.608
Chemoradiation	1.08	0.70	1.65	0.736

Joint Committee on Cancer (AJCC) clinical stage, pathologic variables (regional lymph nodes sampled, positive regional lymph nodes, surgical margins, and pathological stage). Treatment was characterized by surgery type (partial or hemicolectomy, or total colectomy), and adjuvant therapy.

Statistical analysis

Statistical analyses were performed with STATA software (version 12.1, StataCorp, College Station, TX, USA). Patient demographics, disease characteristics, and treatment types were

compared between groups using t-test for continuous variables, and chi square tests for categorical variables. Kaplan-Meier analyses were performed for each T stage and stratified by presence of neural invasion and receipt of chemotherapy and curves were compared using a log-rank test. Median survival time was computed based on the Kaplan-Meier analysis. A Cox proportional hazards model, controlling for patient, disease and treatment covariates, was performed.

Conclusion

PNI is an independent poor prognostic factor in stage T3 and stage T4 colon cancer. Adjuvant chemotherapy in patients with T3–4N0 colon cancer is associated with improved survival in patients with PNI. Further studies are needed to characterize the benefits of specific chemotherapy regimens.

Disclosure of potential conflicts of interest

No potential conflicts of interest were declared.

Disclaimer

The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

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