

# Perineural Invasion Predicts Unfavorable Prognosis in Patients With Invasive Breast Cancer

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**Abstract.** *Background/Aim:* Perineural invasion (PNI) is a poor prognostic factor in a variety of cancers. However, the frequency of PNI in invasive breast carcinoma varies among studies, and the prognostic significance of PNI remains unclear. Therefore, we aimed to explore the prognostic value of PNI in breast cancer patients. *Patients and Methods:* The cohort included 191 consecutive female patients who underwent surgical resection of invasive carcinoma of no special type (NOS). The correlations between PNI and clinicopathological characteristics including prognosis were investigated. *Results:* The frequency of PNI was 14.1% (27/191) and the PNI-positive status was significantly correlated with large pathological tumor size ( $p=0.005$ ), lymph node metastasis ( $p=0.001$ ), and lymphatic invasion ( $p=0.009$ ). The log-rank test showed that PNI-positive patients had shorter distant metastasis-free survival (DMFS) ( $p=0.002$ ) and disease-specific survival (DSS) ( $p<0.001$ ). According to the multivariate analysis, PNI had a significant adverse effect on DMFS ( $p=0.037$ ) and DSS ( $p=0.003$ ). *Conclusion:* PNI could be used as an independent poor prognostic indicator in patients with invasive breast carcinoma.

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*Key Words:* Perineural invasion, breast cancer, prognostic factor, invasive carcinoma of no special type.

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Perineural invasion (PNI) is the process of nerve invasion by cancer cells; however, a consensus regarding the definition is yet to be fully established. To date, the most widely cited definition of PNI is the invasion of tumor cells in, around, and through the nerves (1). However, Veness *et al.* (2) suggested that tumor cells must be present inside the perineural layer in order to call PNI, while Liebig *et al.* (3) proposed that it is appropriate to call PNI when tumor cells are present within any of three layers of the nerve sheath or when tumor foci are present outside of the nerve with the involvement of  $\geq 33\%$  of the nerve's circumference.

Despite the discrepancy regarding the definition of PNI, it has emerged as a key pathological feature for predicting prognosis in many types of cancers, including pancreatic (4), prostate (5), colorectal (6), gastric (7), biliary tract (8), vulvar (9, 10) and cervical cancers (10). In breast cancer, there are few reports investigating the correlation between PNI and prognosis (11-13). In the largest cases series reported by Narayan *et al.*, PNI was found in 15.6% of cases, and it was an independent risk factor for locoregional recurrence (LRR) of invasive breast cancer (11). However, other studies have reported that PNI was found in 25.7% (12) and 1.14% (13) of cases, respectively, and that it had no prognostic value in patients with invasive breast carcinoma. Thus, the frequency of PNI in invasive breast carcinoma varies among studies, and the prognostic significance of PNI remains unclear, to date. Therefore, we aimed to explore the correlation between PNI and distant metastasis-free survival (DMFS) or disease-specific survival (DSS) in patients with invasive breast carcinoma of no special type (NOS) and to determine whether PNI can predict prognosis.

## Patients and Methods

*Patients and tumor specimens.* The cohort comprised 292 consecutive female patients who underwent surgical resection of invasive breast carcinoma that was diagnosed according to the World Health Organization classification of breast cancer (14) from March 2013 to March 2017 at Tottori University Hospital (Yonago, Japan). Among these patients, 66 cases were excluded due to a history of neoadjuvant treatment ( $n=40$ ), bilateral breast cancer

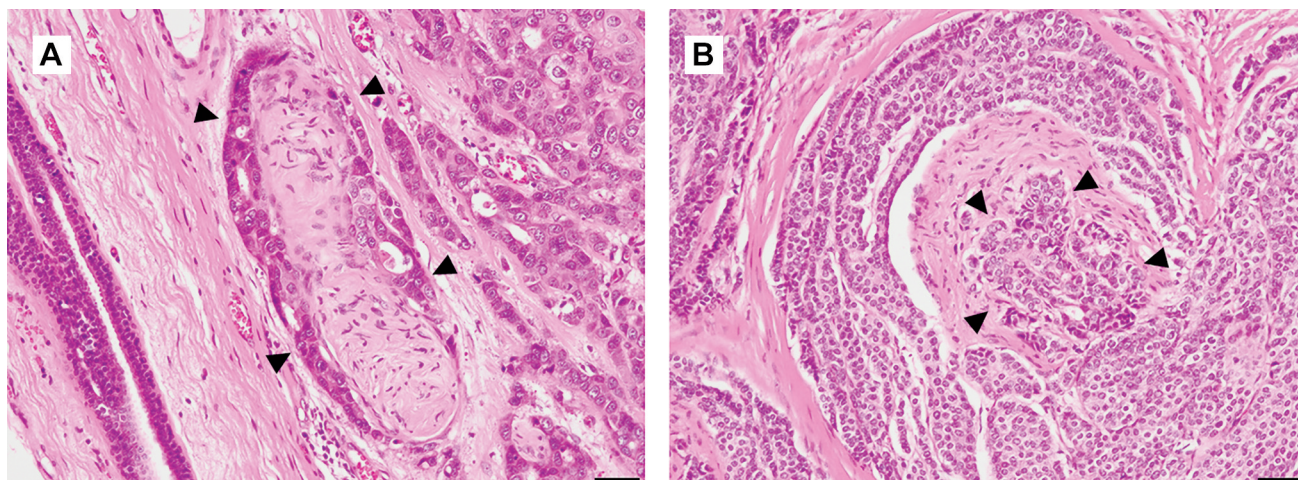


Figure 1. Representative image (hematoxylin and eosin) of perineural invasion in invasive breast carcinoma of no special type. (A) Carcinoma cells are present in close proximity to the nerve in the perineural environment without invasion into the nerve sheath (arrowheads). Scale bar, 25  $\mu\text{m}$ . (B) Carcinoma cells invade the endoneurium (arrowheads). Scale bar, 50  $\mu\text{m}$ .

Table I. Association between perineural invasion and histological or intrinsic subtype of 226 invasive breast carcinomas.

	Total (n=226)	Perineural invasion		p-Value	
		Positive (n=32)	Negative (n=194)		
<b>Histological type</b>					
Invasive carcinoma of no special type	191	27 (14.1%)	164 (85.9%)	0.152	
Invasive lobular carcinoma	15	2 (13.3%)	13 (86.7%)		
Mixed carcinoma	3	1 (33.3%)	2 (66.7%)		
Mucinous carcinoma	10	0	10 (100%)		
Invasive micropapillary carcinoma	2	1 (50%)	1 (50%)		
Metaplastic carcinoma	1	1 (100%)	0		
Solid papillary carcinoma with invasion	3	0	3 (100%)		
Apocrine carcinoma	1	0	1 (100%)		
<b>Intrinsic subtype</b>					
Luminal A-like	117	17 (14.5%)	100 (85.5%)		0.970
Luminal B-like	49	8 (16.3%)	41 (83.7%)		
Luminal B-like (HER2-positive)	32	4 (12.5%)	28 (87.5%)		
HER2-positive (non-luminal)	14	2 (14.3%)	12 (85.7%)		
Triple-negative	14	1 (7.1%)	13 (92.6%)		

HER2, Human epidermal growth factor receptor 2.

(n=15), microinvasive carcinoma (n=7), distant metastasis (n=3) and short follow-up period (n=1). Thus, 226 patients were included in the first analysis. Of the included patients, 191 patients with invasive carcinoma of NOS were analyzed for clinicopathological characteristics and prognostic value. Clinicopathological data of the patients were obtained from the hospital medical records. Data regarding the histopathological factors, including the lymph node metastasis, Ki67 labeling index (LI), estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) statuses, were retrieved from the pathology reports. Histological grade was determined according to the Elston–

Ellis’s criteria (15). ER-positive or PgR-positive status was defined as  $\geq 1\%$  of immunoreactive cells. HER2-positive status was determined based on the Hercep Test (Dako Agilent Technology, Santa Clara, CA, USA) scored 3+. Cases that scored 2+ were considered as HER2-positive when the presence of HER2 amplification was detected through a fluorescent in situ hybridization analysis using PathVysion kit (Abott-Vysis, Inc., Downers Grove, IL, USA). Written informed consent was obtained from all the participants, and this study was approved by the Ethics Committee of the Faculty of Medicine, Tottori University (approval number: 22A038; approval date: 9 August 2022).

**Evaluation of PNI.** Hematoxylin and eosin tissue sections were used for the detection of PNI by two pathologists (K.H. and Y.U.). PNI was defined as the presence of carcinoma cells within any of the three layers of the nerve sheath (11).

**Statistical analysis.** Categorical variables are presented as count and percentage; continuous variables are presented as mean±standard deviation. The association between PNI status and clinicopathological factors was evaluated using non-parametric tests; chi-square and Fisher's exact tests were used for categorical variables. For the survival analysis, two different endpoints, cancer relapse (distant metastatic recurrence) and cancer-related death were used to calculate DMFS and DSS, respectively. DMFS was defined as the period from the date of initial surgery to the date of clinical or pathological cancer relapse with distant metastasis. DSS was defined as the period from the date of initial surgery to the date of cancer-related death. Patients were censored at the time of their last cancer-free follow-up or at the time of death due to reasons unrelated to breast cancer. Survival curves were computed based on the Kaplan-Meier method and tested statistically using the log-rank test. The Cox proportional hazard regression model was used to perform univariate and multivariate analyses of several factors associated with DMFS and DSS. All tests were two-sided, and *p*-values of <0.05 were considered statistically significant in all tests. All statistical analyses were performed using the SPSS version 25 software (IBM SPSS Statistics; IBM Corporation, Armonk, NY, USA).

## Results

**Correlation between PNI and histological type or intrinsic subtype.** A representative hematoxylin and eosin image of PNI is shown in Figure 1. The frequency of PNI was 14.2% (32/226) in invasive breast carcinoma cases. Of 32 cases with PNI, 27 (84.4%) were invasive carcinoma of NOS (Table I). No significant difference was observed in the frequency of PNI status according to histological type (*p*=0.152) or intrinsic subtypes (*p*=0.970) (Table I).

**Clinicopathological characteristics and associations with PNI status.** The clinicopathological characteristics of the 191 patients with invasive carcinoma of NOS are summarized in Table II. Mastectomy and breast-conserving surgery were performed in 87 (45.5 %) and 104 patients (54.5%), respectively. Additionally, 109 (57.1%) and 73 patients (38.2%) received radiation therapy and chemotherapy, respectively. The frequency of PNI was 14.1% (27/191) and PNI-positive status was significantly correlated with large pathological tumor size (*p*=0.005), the presence of lymph node metastasis (*p*=0.001), and lymphatic invasion (*p*=0.009) (Table III).

**Survival analysis according to PNI status.** The median follow-up period was 70 months (range=5-104). Twenty-six patients (13.6%) experienced metastatic recurrence, 18 patients (9.4%) died due to breast cancer progression and 14 patients (7.3%)

Table II. *Clinicopathological characteristics of 191 invasive breast carcinomas of no special type.*

Factors	Numbers	%
Patient age (mean±SD, years)	62.4±13.0	
Pathological tumor status		
pT1	127	66.5
pT2	53	27.7
pT3	4	2.1
pT4	7	3.7
Pathological node status		
pN0	142	74.3
pN1	36	18.9
pN2	10	5.2
pN3	3	1.6
Histological grade		
I	65	34.0
II	74	38.7
III	52	27.2
Estrogen receptor		
Positive	162	84.8
Negative	29	15.2
Progesterone receptor		
Positive	151	79.1
Negative	40	20.9
HER2 status		
Positive	41	21.5
Negative	150	78.5
Ki67 labeling index		
≤30%	124	64.9
>30%	67	35.1
Subtype		
Luminal A-like	97	50.8
Luminal B-like	40	20.9
Luminal B-like (HER2-positive)	28	14.7
HER2-positive (non-luminal)	13	6.8
Triple Negative	13	6.8
Chemotherapy		
None	118	61.8
Performed	73	38.2

HER2, Human epidermal growth factor receptor 2.

died due to causes, such as other cancers (n=3), pneumonia (n=4), cardiovascular disease (n=2), cerebral hemorrhages (n=2) and others causes (n=3). The DMFS and DSS curves are shown in Figure 2. The log-rank test showed that patients with PNI-positive status had significantly shorter DMFS (*p*=0.002) and DSS (*p*<0.001). The 5-year DMFS rates in the PNI-positive and PNI-negative groups were 69.0% [95% confidence interval (CI)=0.456–0.839] and 89.9% (95% CI=0.840–0.937), respectively, whereas the 5-year DSS rates in these groups were 74.5 % (95% CI=0.517–0.877) and 93.7% (95% CI=0.885–0.965), respectively.

The univariate analysis revealed a significant correlation between shorter DMFS and PNI-positive status (*p*=0.003), large pathological tumor size (*p*<0.001), high histological

Table III. Association between perineural invasion and clinicopathological characteristics of 191 invasive breast carcinomas of no special type.

Factors	Total (n=191)	Perineural invasion		p-Value
		Positive (n=27)	Negative (n=164)	
Patient age (years)				
≤50	39	5	34	0.995
>50	152	22	130	
Pathological tumor size (mm)				
≤20	127	11	116	0.005
>20	64	16	48	
Histological grade				
I+II	139	20	119	0.870
III	52	7	45	
Lymph node metastasis				
Present	49	14	35	0.001
Absent	142	13	129	
Lymphatic invasion				
Present	58	14	44	0.009
Absent	133	13	120	
Estrogen receptor				
Positive	162	24	138	0.525
Negative	29	3	26	
Progesterone receptor				
Positive	151	25	126	0.062
Negative	40	2	38	
HER2 status				
Positive	41	4	37	0.364
Negative	150	23	127	
Ki67 labeling index				
<30%	124	16	108	0.506
≥30%	67	11	56	
Chemotherapy				
None	118	17	101	0.891
Performed	73	10	63	

HER2, Human epidermal growth factor receptor 2.

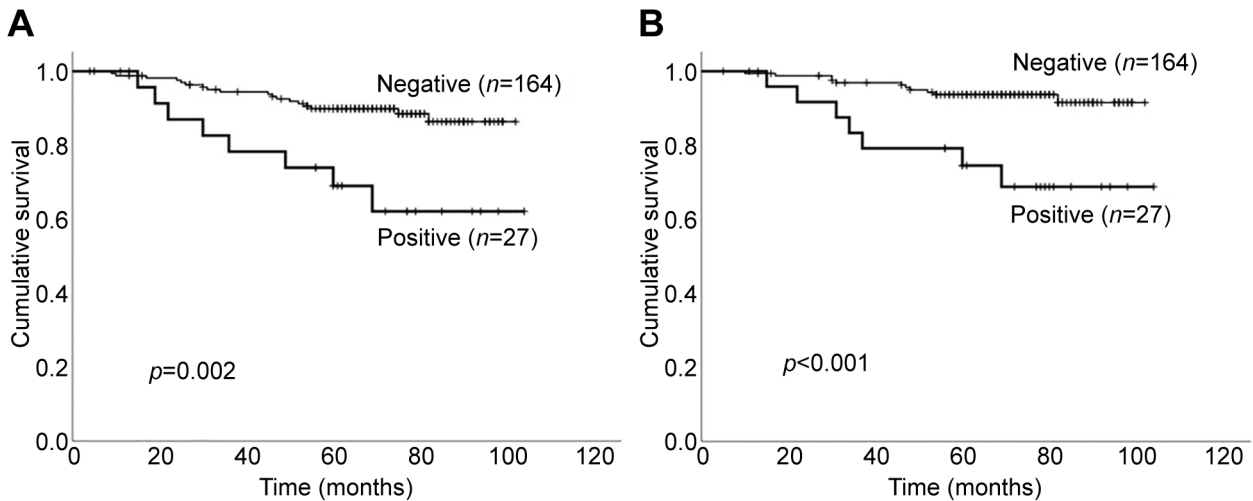


Figure 2. Kaplan-Meier survival curve for distant metastasis-free survival (A) and disease-specific survival (B) in 191 patients with invasive carcinoma of no special type.

Table IV. Univariate and multivariate analyses of various prognostic factors for distant metastasis-free survival in 191 invasive breast carcinomas of no special type.

Prognostic factors	Univariate			Multivariate		
	HR	95% CI	<i>p</i> -Value	HR	95% CI	<i>p</i> -Value
Patient age (years)						
>50 vs. ≤50	2.014	0.632-7.009	0.226			
Pathological tumor size (mm)						
>20 vs. ≤20	4.287	1.910-9.623	<0.001	2.537	1.051-6.124	0.038
Histological grade						
III vs. I+II	3.918	1.798-8.537	<0.001	3.293	1.195-9.078	0.021
Estrogen receptor						
Negative vs. positive	1.778	0.713-4.432	0.217			
Progesterone receptor						
Negative vs. positive	1.475	0.620-3.510	0.380			
HER2						
Positive vs. negative	1.083	0.435-2.700	0.864			
Ki-67 labeling index						
≥30 vs. <30	2.718	1.247-5.924	0.012	0.890	0.318-2.492	0.824
Lymph node metastasis						
Present vs. absent	3.017	1.394-6.533	0.005	1.557	0.649-3.738	0.321
Perineural invasion						
Positive vs. negative	3.471	1.509-7.987	0.003	2.621	1.060-6.477	0.037
Chemotherapy						
None vs. performed	0.989	0.449-2.180	0.978			

HR, Hazards ratio; CI, confidence interval; HER2, human epidermal growth factor receptor 2.

grade ( $p < 0.001$ ), high Ki67 LI ( $p = 0.012$ ) and the presence of lymph node metastasis ( $p = 0.005$ ) (Table IV). According to the multivariate analysis, PNI-positive status had a significant effect on DMFS [hazard ratio (HR)=2.621;  $p = 0.037$ ], as well as large pathological tumor size (HR=2.537;  $p = 0.038$ ), and high histological grade (HR=3.293;  $p = 0.021$ ) (Table IV). The univariate analysis showed a significant correlation between shorter DSS and PNI-positive status ( $p = 0.001$ ), large pathological tumor size ( $p = 0.043$ ), and negative-ER status ( $p = 0.031$ ) (Table V). The multivariate analysis showed that PNI-positive status had a significant adverse effect on DSS (HR=4.463;  $p = 0.003$ ), as well as negative ER status (HR=3.234;  $p = 0.022$ ) (Table V).

## Discussion

Although there have been several studies to date evaluating the role of PNI as a potential predictor of prognosis in various cancers, the clinical significance of PNI in patients with breast carcinoma remains controversial. In the present study, we aimed to clarify the prognostic value of PNI in invasive breast carcinoma and revealed that PNI was an independent poor prognostic factor for DMFS and DSS.

The frequency of PNI in invasive breast cancer varies from 1.14% to 34.2% according to previous studies (11-13, 16). The main reason for the discrepancy in the PNI

frequency among these studies may be the difference in cohort sizes and detection methods. In the present study, the incidence of PNI was 14.1%, which is similar to that in the largest case series (15.6%) reported by Narayan *et al.* (11). To our knowledge, the present study was the first to find that there were no significant differences in the incidence of PNI according to intrinsic subtypes of breast carcinoma.

Duraker *et al.* reported that vascular invasion, axillary lymph node, and PgR positivity ratios were significantly higher in PNI-positive patients than in the PNI-negative ones (12). Kapak *et al.* reported that PNI was associated with higher T-stages, higher tumor grades, and lymphovascular invasion (LVI) (13). We also found that PNI-positive status was significantly correlated with large pathological tumor size, the presence of lymph node metastasis, and lymphatic invasion. It has been considered that PNI is a potential pathway for dissemination and metastasis of carcinoma cells in the same way as lymphatic and vascular channels (17). Additionally, it has been suggested that PNI can be observed before LVI (3) and that it is a pathway that eventually leads to lymphatic invasion (18). Angiogenesis and neurogenesis share a number of similarities and both processes are regulated by similar neurotrophic factors and transmitters (19); therefore, further studies are needed to clarify the relationship between PNI and LVI in invasive breast

Table V. Univariate and multivariate analyses of various prognostic factors for disease-specific survival in 191 invasive breast carcinomas of no special type.

Prognostic factors	Univariate			Multivariate		
	HR	95% CI	p-Value	HR	95% CI	p-Value
Patient age (years)						
>50 vs. ≤50	2.160	0.497-9.394	0.305			
Pathological tumor size (mm)						
>20 mm vs. ≤20	2.609	1.029-6.612	0.043	1.766	0.667-4.678	0.252
Histological grade						
III vs. I+II	2.153	0.850-5.458	0.106			
Estrogen receptor						
Negative vs. positive	2.953	1.106-7.887	0.031	3.234	1.184-8.832	0.022
Progesterone receptor						
Negative vs. positive	2.004	0.752-5.346	0.165			
HER2						
Positive vs. negative	1.024	0.337-3.113	0.966			
Ki-67 labeling index						
≥30 vs. <30	1.513	0.596-3.841	0.383			
Lymph node metastasis						
Present vs. absent	2.077	0.804-5.362	0.131			
Perineural invasion						
Positive vs. negative	4.672	1.810-12.060	0.001	4.463	1.641-12.140	0.003
Chemotherapy						
None vs. performed	2.311	0.761-7.024	0.140			

HR, Hazards ratio; CI, confidence interval; HER2, human epidermal growth factor receptor 2.

carcinoma. In future studies, we plan to investigate whether PNI is an independent prognostic factor in node-negative breast cancer patients, since lymphatic invasion was considered to be the only significant predictor of distant recurrence in these patients (20).

Many reports have concluded that PNI is a poor prognostic factor in several types of cancers (4-10). To our knowledge, there are few reports that have investigated the direct relationship between PNI and prognosis in breast cancer patients (11-13). Duraker *et al.* reported that PNI had no prognostic value in patients with invasive breast carcinoma; however, the cohort in their study is relatively outdated (from 1996 to 1999), and the study was conducted before the emergence of anti-HER2 therapy. Moreover, the frequency of ER and PgR positivity was very low (48.8% and 50.2%, respectively). Although the incidence of PNI was very low (1.14%), Karak *et al.* also stated that the significance of PNI as an independent poor prognostic factor remains questionable (13). Contrary, the largest case series reported by Narayan *et al.* revealed that PNI was an independent risk factor for LRR in invasive breast cancer and that the increased risk caused by PNI was similar in magnitude to that observed in the case of LVI or ER/PgR negativity (11). They pointed out that the reliability of detecting nodal recurrences before the appearance of distant

metastases is uncertain. Therefore, we used DMFS, instead of LRR as recurrence-related endpoint. Although the number of patients in our study is very small compared to that in the report by Narayan *et al.*, our study revealed, for the first time, that PNI was an independent unfavorable prognostic factor for DMFS and DSS.

The limitations of our study included the small sample size, its retrospective nature, and that the therapeutic methods were not the same among patients. Future studies that stratify the patients by the intrinsic subtype, pathological stage, or nodal status are warranted to clarify the importance of PNI as a prognostic factor in breast carcinoma.

### Conclusion

This is the first study to demonstrate that PNI is an independent poor prognostic factor for DMFS and DSS in patients with invasive breast carcinoma. Although further studies with large size cohorts are necessary, our findings suggest that PNI could be useful in predicting aggressive phenotypes in breast cancer patients.

### Conflicts of Interest

The Authors declare that there are no conflicts of interest regarding this study.

## Authors' Contributions

Conception and design: K.H., M.W. and Y.U.; acquisition of data: K.H. and M.W.; analysis and interpretation of data: K.H., M.W., K.I., and Y.U.; and writing, review, and/or revision of the manuscript: K.H., M.W., K.I. and Y.U. All Authors read and approved the final version.

## Acknowledgements

The Authors are grateful to Kazuko Fukushima for their excellent technical assistance with the processing of the pathological specimens.

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Received November 9, 2022

Revised December 9, 2022

Accepted December 13, 2022