Prognostic Role of Lymphovascular Invasion and Perineural Invasion in Breast Cancer Treated with Neoadjuvant Chemotherapy

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ABSTRACT

In our study, we investigated the predictive properties of LVI (lymphovascular invasion) and PNI (perineural invasion) on survival times from pathology specimens obtained from surgical operation after neoadjuvant chemotherapy (NAC) with breast cancer patients. Two hundered eleven female patients were included in this study. We evaluated the relationship between potential prognostic factors and mean recurrence-free survival (RFS) and overall survival (OS) times using Kaplan-Meier methodology and Cox proportional hazard modelling.The mean follow-up time was 27.3 months.PNI positive patients had shorter RFS and OS times than PNI negatives (p< 0.001, p= 0.002, respectively), and LVI positive patients had shorter RFS and OS times than LVI negatives (p< 0.001, p< 0.001, respectively). In the multivariate analysis performed, the presence of pN stage and PNI were found to be predictive for RFS (p= 0.047, p< 0.001, respectively), while pT stage and PNI positivity were found to be predictive for OS (p= 0.035, p= 0.017, respectively). LVI did not show the property of being an independent predictive marker for survival. PNI caused significant survival differences in all subtypes for both RFS (log-rank p< 0.001, p= 0.003, p= 0.001, respectively) and OS(log-rank p= 0.035, p= 0.006, p= 0.020 respectively) in HR+/Her2-, Her2+ and Triple negative breast cancer subtyping. LVI, on the other hand, caused survival distribution difference for RFS (p= 0.021) in the HR+/Her2- subtype and for both RFS and OS in the Triple-negative subtype (p< 0.001, p= 0.025, respectively). PNI is strongly and significantly associated with RFS and OS. We suggest that it can be used in identifying high-risk patients for recurrence of PNI and in new staging systems.

Keywords: Lymphovascular, Perineural, Neoadjuvant, Breast cancer, Prognostic

INTRODUCTION

According to 2021 data, if skin cancers are excluded, breast cancer is the most common type of cancer worldwide and the most common cause of death in women.[1] Neoadjuvant (NAC) chemotherapy is one of the preferred treatment methods in inflammatory and locally advanced breast cancer because it provides axillary down staging reaching 40%, allows breast sparing surgery, and provides in-vivo manifestation of chemotherapy response.[2-4] Due to the different phenotypes of breast cancer that show histopathological and molecular variability, the NAC response is also variable and this causes the prognosis to be different. Many prognostic factors such as body-mass index, axillary lymph node metastasis, tumor grade, Ki-67 proliferation index, tumor size, lymphovascular invasion (LVI) have been reported in studies.[5-8]

Perineural invasion (PNI) is defined as the invasion of the neural fascicles or perineurium around the tumor by cancerous cells.[9] It is known to be prognostic especially for pancreatic, biliary tract, prostate, colon, rectum and stomach cancer types.[10-14]

LVI is expressed as the appearance of tumor cells in blood vessels or lymphatics.[15] Classical distant metastasis pathway is spread through the blood vessels and lymphatic system, but PNI, which is a different pathway from the known paradigm, is also considered as an important pathway for local recurrence and distant metastasis.[16] In general, PNI and LVI often co-occur, and LVI is also positive in up to 54% of PNI-positive patients.[17] Due to this frequent association and discussed histopathological similarities, PNI, which has few studies supporting its prognostic feature alone, is considered to be prognostic together with LVI in breast cancer, but not an independent prognostic factor alone.[9,18,19]

In this study, while examining the prognostic factors in breast cancer patients receiving neoadjuvant chemotherapy, we aimed to investigate the effects of PNI and LVI, which have limited studies, on survival. We investigated the potential impact of PNI and LVI on the risk of relapse and death in patients who have received NAC, and explored their properties as ideal markers for risk-adjusted follow-up and treatment planning.

PATIENTS and Methods

Patients

We retrospectively reviewed the medical records of patients who received NAC and subsequently underwent surgery between January 2013 and January 2021, after obtaining institutional ethics committee approval. Pre-NAC breast magnetic resonance visualization, breast ultrasound, and positron emission tomography-computed tomography were used to identify and stage distant metastases and contralateral breast lesions. Inclusion criteria were as follows: aged > 18 years old, female sex, primary tumor size ≥ 5 cm or lymph node metastasis, inflammatory breast cancer and implementation of the entire planned NAC regimen. The exclusion criteria were the presence of a previous or concomitant second malignancy history, the absence of pathology and clinicopathological data in our hospital system and presence of distant metastases at the time of diagnosis. All cases were discussed at The Institutional Multidisciplinary Tumor Board. 8 of the 242 patients analyzed had distant organ metastasis at the first diagnosis, 6 patients had accompanying second malignancy, 8 patients failed to complete the NAC protocol, and 9 patients were found to have ex malignancy from external causes, for these reasons these patients were excluded from the study, and a total of 211 patients were included in the study.

Treatment

All of the included patients received either docetaxel (75 mg/m^2) every 3 weeks for 4 cycles or paclitaxel (80 mg/m^2) once every 12 cycles after 4 cycles of cyclophosphamide and anthracycline (epirubicin or doxorubicin) combination. In case of human epidermal growth factor receptor 2 positive (Her2+), trastuzumab (±pertuzumab; patients who received pertuzumab only received 4 cycles in the NAC period) in the neoadjuvant period. Surgically, patients underwent breast-conserving surgery or modified radical mastectomy, axillary dissection, or sentinal lymph node sampling. Postoperative trastuzumab (without pertuzumab) use was completed in one year in all Her2+ patients. Hormone receptor positive (HR+) patients were treated with hormone therapy after surgery and adjuvant radiotherapy was given to eligible patients in collaboration with a radiation oncologist.

Pathology

Pathological complete response (pCR) was considered as the absence of histopathological evidence of residual cancer cells in the breast and axillary lymph nodes.[20] In patients with a pCR response, pre-NAC histological type and molecular subtyping were accepted. Histological grouping was done as two groups as ductal type and others. According to the guide of the American Society of Clinical Oncology/College of American Pathologists, those with ER (estrogen receptor) and PgR (progesterone receptor) above 1% were considered positive.[21] Those who had a cerbb2 score of +3 after immunohistochemical (IHC) analysis and those who were +2 and positive by fluorescence in situ hybridization (FISH) analysis were considered Her2+. The pathology laboratory of our hospital reported the Ki-67 cut-off value as "18" for luminal separations and this cut-off was used in the statistical analy-

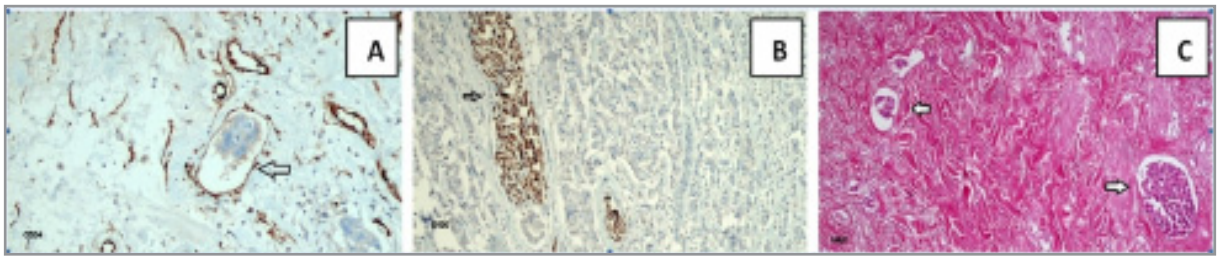

Figure 1. Lymphovascular invasion and perineural invasion in invasive breast cancer in H&E and immunostained slides. A)Lymphovascular invasion with tumour cells (arrow) seen in CD34 stained; x400. B)Perineural invasion with tumour cells (arrow) seen in S100 stained; x400. C)Lymphovascular invasion (right white arrow) seen in H&E and perineural invasion (left white arrow) stained sections of breast tumors from the same case; x400.

sis. Tumor pathological staging was performed according to the AJCC TNM classification.[22] Based on prior studies, subtype groups were defined as a) hormone receptor positive (ER and/or PgR positive) and Her2 negative, b) Her2 positive regardless of hormonal status, and c) Triple negative (ER, PgR, and Her2 negative).[23]

Definition of LVI and PNI

The LVI and PNI were re-examined by the pathology specialist of our hospital and specimens that obtained from the operations performed after NAC were reported for second time. LVI positivity was defined as the presence of tumor cells within an endothelium-lined space (lymphatics or blood vessels) with hematoxylin-eosin staining and IHC as shown in Figure 1 on surgical slides after NAC. Specific markers (D2-40, CD34) were used in suspicious cases.

PNI was evaluated as positive in the presence of cancer cells in the perineurium or nerve fascicles in the mammary parenchyma after IHC analysis with hematoxylin-eosin. Specific marker (S100) was used in suspicious cases. IHC images for PNI and LVI are shown in Figure1.

Statistical Analysis

Times of recurrence-free survival (RFS) and overall survival (OS) were calculated from date of initial surgery to date of first event or death or last follow-up (in cases without events). Survival analysis were performed using the Kaplan-Meier method and the Log-Rank test was used for group comparison. Univariate vs multivariate analysis of factors affecting survival were created with the Cox Proportional-Hazards Model. All statistical analyses were performed using SPSS version 26.0 (IBM Corb, Armonk, NY). Statistical significance defined as a P value< 0.05.

This study was approved by Ethical Committee of Tekirdag Namik Kemal University (date: 29.06.2021, approvel number: 2021.179.06.09).

RESULTS

Patient and Tumor Baseline Characteristics

A total of 211 patients were examined. All of them consisted of female patients, median age was 50 years (range 24-76). 47 (22.3%) patients had recurrence (local or distant metastasis) during the follow-up period. 18 (8.5%) of all study patients died due to cancer-related reasons. Mean follow-up was 27.3±18.1 months (range 3.3-81.6).

84 (39.8%) patients had LVI positivity, 57 (27.0%) patients had PNI positivity. In the classification made considering the receptor status, 121 (57.3%) patients were HR+/Her2-, 62 (29.4%) patients were Her2+ and 28 (13.3%) were Triple negative subtypes (Table 1).

Recurrence-Free Survival (RFS) Analysis

The LVI positive group had a significantly shorter RFS (3-year, 5-year survival rates: 61.2%, 33.6% vs 84.7%, 75.9%, respectively) than the LVI negative group. Similarly, the PNI positive group had a significantly shorter RFS (3-year, 5-year survival rates: 51.6%, 14.7% vs 83.1%, 73.1%, respectively) than the PNI negative group. The mean RFS (mRFS) in all patients was 61.0±3.5 months (95%

Table 1. Clinicopathological features and rates of patients

Clinicopathological characteristics	n (%)
Age	
< 40 (Young Adult)	44 (20.9%)
≥ 40	167 (79.1%)
Menapausel status	
Premenopausal	100 (47.4%)
Postmenopausal	111 (52.6%)
Histologictype	
Ductal	179 (84.8%)
Others	32 (15.2%)
PgRstatus	
Negative	70 (33.2%)
Positive	141 (66.8%)
ER status	
Negative	47 (22.3%)
Positive	164 (77.7%)
Her2 status	
Negative	150 (71.1%)
Positive	61 (28.9%)
Ki-67	
< 18	55 (26.1%)
≥ 18	156 (73.9%)
Histologic Grade	
Grade ≤ 2	149 (70.6%),
Grade 3	62 (29.4%)
Pathologic T stage	
T0/T1-T2/T3/T4	63 (29.9%), 94 (44.5%), 43 (20.4%), 11 (5.2%)
Pathologic N stage	
N0/N1/N2/N3	107 (50.7%), 59 (28%), 34 (16.1%), 11 (5.2%)
LVI status	
Negative	127 (60.2%)
Positive	84 (39.8%)
PNI status	
Negative	154 (73.0%)
Positive	57 (27.0%)
pCR	
Negative	161 (76.3%)
Positive	50 (23.7%)
Axillary Dissection	
Negative	59 (28%)
Positive	152 (72%)

Her2= Human epidermal growth factor receptor 2; ER= Estrogene receptor; PgR= Progesterone receptor; LVI= Lymphovacular invasion; PNI= Perineural invasion; pCR= Pathologic complete response

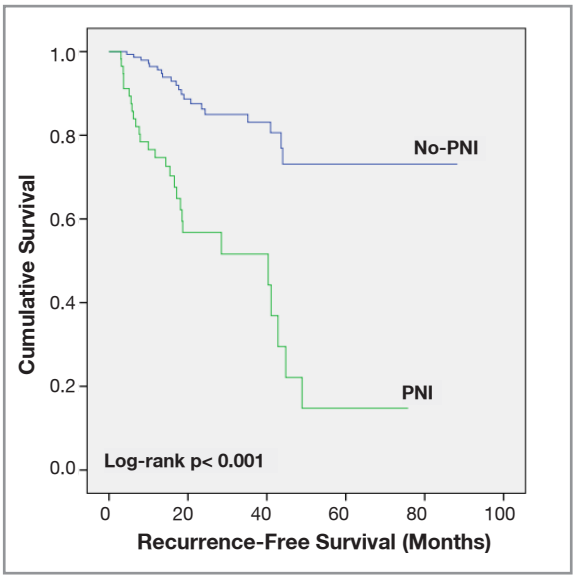

Figure 2. Relationship between PNI and RFS

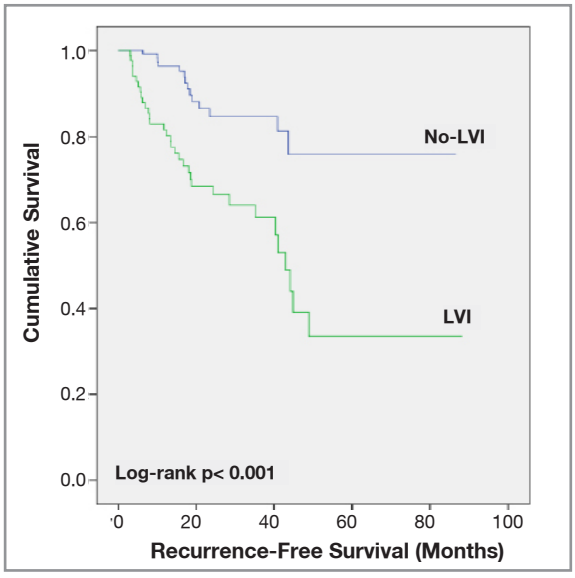

Figure 3. Relationship between LVI and RFS

CI: 54.2-67.9). mRFS was 47.1±5.0 months in LVI positive patients, 72.0±3.8 months in LVI negative patients, 33.3±4.3 months in PNI positive patients, and 71.9±3.5 months in negative patients (log-rank p< 0.001, p= 0.001, respectively) (Figures 2, 3).

In the created univariate cox regression model, pT stage (HR= 1.70, 95% CI: 1.23-2.28, p= 0.001), pN stage (HR= 1.74, 95% CI: 1.32-2.29, p< 0.001), pCR status (HR= 0.33, 95% CI: 0.13-0.83,

Table 2. Univariate and Multivariate analyses of factors for Recurrence-Free Survival (RFS)

		Univariate analysis		Multivariate analysis	
Variable	**Category**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P[f]**
Age	< 40 / ≥ 40	1.58 (0.67-3.73)	0.296		
Menopausal Status	Pre/Post	1.10 (0.61-1.97)	0.761		
Histologic type	Ductal/Others	1.45 (0.70-3.01)	0.314		
PgR Status	Negative/Positive	0.94 (0.51-1.74)	0.845		
ER Status	Negative/Positive	0.87 (0.44-1.71)	0.682		
Ki67	< 18 / ≥ 18	1.40 (0.73-2.67)	0.313		
Her2 Status	Negative/Positive	0.88 (0.45-1.73)	0.710		
Grade	≤ 2/3	1.45 (0.85-2.50)	0.177		
pT Status	T0-T2/T3-T4	1.70 (1.23-2.28)	0.001		
pN Status	N0/N1-N3	1.74 (1.32-2.29)	< 0.001	1.39 (1.01-1.92)	0.047
LVI	Negative/Positive	3.57 (1.91-6.68)	< 0.001		
PNI	Negative/Positive	4.84 (2.71-8.65)	< 0.001	3.78 (2.02-7.09)	< 0.001
Axiller Disection	Negative/Positive	2.22 (0.93-5.27)	0.072		
pCR	Negative/Positive	0.33 (0.13-0.83)	0.018		

s Significant values are indicated in bold. Pf: Forward:LR method
Her-2, Human epidermal growth factor receptor 2; ER, estrogene receptor; PgR, Progesterone receptor; LVI, Lymphovascular invasion; PNI, Perineural invasion; pCR, Pathologic complete response.

p= 0.018), LVI (HR= 3.57, 95% CI: 1.91-6.68, p<0.001), and PNI (HR= 4.84, 95% CI: 2.71-8.65, p< 0.001) were found to be factors associated with RFS (Table 2).

Factors predicting survival were evaluated with the multivariate cox regression model. In the model created, pN stage (HR= 1.39, 95% CI: 1.01-1.92, p= 0.047) and PNI positivity (HR= 3.78, 95% CI: 2.02-7.09, p< 0.001) continued to be predictive for RFS. The statistical significance of pCR, pT stage, and LVI could not be demonstrated in multivariate analysis (Table 2).

Overall Survival (OS) Analysis

The LVI positive group had a significantly shorter OS (3-year, 5-year survival rates: 84.7%, 74.7% vs 92.8%, 90.2%, respectively) than the LVI negative group. Similarly, the PNI positive group had a significantly shorter OS (3-year, 5-year survival rates: 79.8%, 62.7% vs 92.6%, 89.6%, respectively) than the PNI negative group. The mean OS (mOS) in all patients was 74.3±3.2 months (95% CI, 68.0-80.6). The mOS was 67.4±4.7 months in LVI positive patients, 80.8±2.5 months in LVI negative patients, 57.8 ±5.2 months in PNI positive patients, and 82.1±2.3 months in negative patients (log-rank p= 0.028, p< 0.001, respectively) (Figures 4, 5).

In the created univariate cox regression model, pT stage (HR= 2.14, 95% CI: 1.29-3.56, p= 0.003), pN stage (HR= 1.61, 95% CI: 1.01-2.56, p= 0.046), LVI (HR= 3.02, 95% CI: 1.07-8.51, p= 0.036) and PNI (HR= 4.70, 95% CI: 1.82-12.13, p= 0.001) were found to be factors associated with OS (Table 3).

Factors predicting survival were evaluated with the multivariate cox regression model. In the model created, pT status (HR= 1.85, 95% CI: 1.05-3.26, p= 0.035) and PNI positivity (HR= 3.30, 95% CI: 1.23-8.78, p= 0.017) provided independent predictive properties for mOS. The statistical significance of pN stage and LVI in the multivariate analysis could not be demonstrated (Table 3).

The Survival Relationship of PNI and LVI According to Breast Cancer Subtypes

There were significant differences in the distribution of molecular subgroups by LVI status accord-

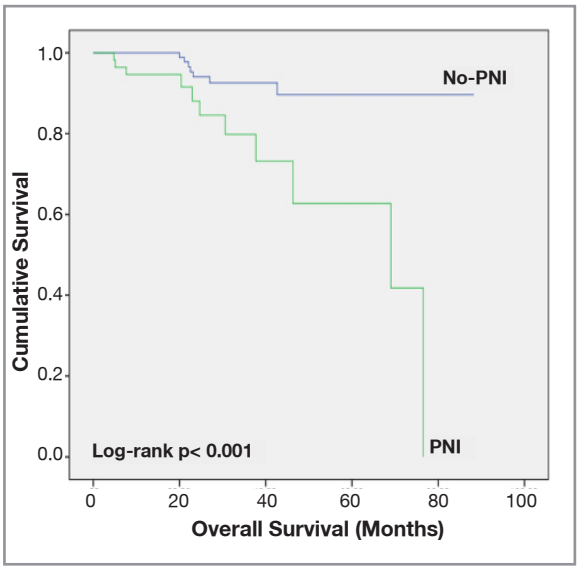

Figure 4. Relationship between PNI and OS

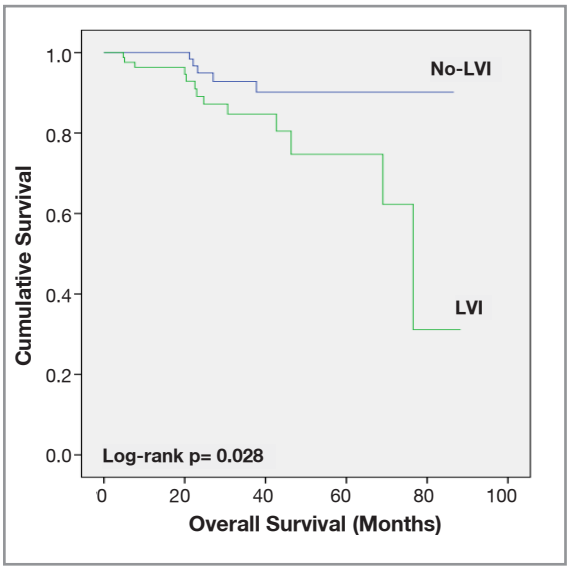

Figure 5. Relationship between LVI and OS

ing to RFS in HR+/Her2- and Triple negative subtypes (log-rank p= 0.021, p< 0.001, respectively). There was no relationship between LVI and RFS in the Her2+ group (log-rank p= 0.089). When analyzed according to OS, LVI created a significant difference in triple negative subtype (log-rank p= 0.025), while the statistical significance of LVI could not be demonstrated in HR+/Her2- and Her2+ subtypes (log-rank p= 0.278, p= 0.486, respectively) (Table 4).

Table 3. Univariate and Multivariate analyses of factors for Overall Survival (OS)

		Univariate analysis		Multivariate analysis	
Variable	**Category**	**HR (95% CI)**	**P**	**HR (95% CI)**	**Pf**
Age	< 40 / ≥ 40	0.79 (0.26-2.40)	0.675		
Menopausal Status	Pre/Post	0.71 (0.28-1.81)	0.478		
Histologic type	Ductal/Others	1.10 (0.32-3.82)	0.882		
PgR Status	Negative/Positive	0.58 (0.23-1.48)	0.257		
ER Status	Negative/Positive	0.46 (0.17-1.26)	0.130		
Ki67	< 18 / ≥ 18	2.14 (0.70-6.57)	0.182		
Her2 Status	Negative/Positive	0.48 (0.11-2.11)	0.331		
Grade	≤ 2/3	1.45 (0.59-3.56)	0.416		
pT Status	T0-T2/T3-T4	2.14 (1.29-3.56)	0.003	1.85 (1.05-3.26)	0.035
pN Status	N0/N1-N3	1.61 (1.01-2.56)	0.046		
LVI	Negative/Positive	3.02 (1.07-8.51)	0.036		
PNI	Negative/Positive	4.70 (1.82-12.13)	0.001	3.30 (1.23-8.78)	0.017
Axiller Disection	Negative/Positive	3.82 (0.50-29.16)	0.196		
pCR	Negative/Positive	0.18 (0.02-1.38)	0.099		

sSignificant values are indicated in bold. Pf: Forward:LR method
HER-2, Human epidermal growth factor receptor 2; ER, Estrogene receptor; PgR, Progesterone receptor; LVI, Lymphovascular invasion; PNI, Perineural invasion; pCR, Pathologic complete response.

Table 4. Survival analysis results of perineural invasion and lymphovascular invasion by breast cancer subtypes

	HR+/HER2-	Her2+	Triple negative
Total	121	62	42
PNI			
Number of PNI positive (%)	37 (30.6%)	14 (22.6%)	6 (21.4%)
Number of PNI negative (%)	84 (69.4%)	48 (77.4%)	22(78.6%)
P value for RFS	< 0.001	0.003	0.001
P value for OS	0.035	0.06	0.020
LVI			
Number of LVI positive (%)	58 (47.9%)	17 (27.4%)	9 (30.9%)
Number of LVI negative (%)	63 (52.1%)	45 (72.6%)	19 (69.1.9%)
P value for RFS	0.021	0.089	< 0.001
P value for OS	0.278	0.486	0.025

sSignificant values are indicated in bold
Her2, Human epidermal growth factor receptor 2; HR, Hormone receptor; PNI, Perineural invasion; LVI, Lymphovascular invasion; RFS, Recurrence-free survival; OS, Overall survival

When breast cancer subtypes were analysed according to PNI, both RFS (log-rank p< 0.001, p= 0.003, p= 0.001) and OS (log-rank p= 0.035, p= 0.006, p= 0.020, respectively) demonstrated survival difference in all of the HR+/Her2-, Her2+, and triple-negative subtypes' survival curves (Table 4).

DISCUSSION

We investigated the prognostic significance of PNI and LVI on survival in breast cancer patients receiving NAC. It was observed that patients with positive PNI have a 3.78 times greater risk of recurrence and a 3.3 times greater risk of death than patients with negative. pN stage with PNI provided predictive features for RFS and pT stage with PNI provided predictive features for OS when potential prognostic variables associated with survival were examined with the multivariate model. With this study, it was concluded that PNI can be used as a strong prognostic marker predicting both RFS and OS, but LVI does not have the feature of being an independent predictive marker.

The first studies in the literature, which are out of date, did not find a prognostic significance of the presence of PNI, but in their study Karak et al. evaluated PNI as a prognostic marker in their study, which included only 13 PNI-positive patients.[9,24,25] Similarly, in Koca et al.'s study, which included only patients who received adjuvant treatment, and Sahoo et al.'s study, which included patients who received adjuvant or neoadjuvant treatment, PNI was shown to be a prognostic marker predicting RFS and OS.[26,27] In a large cohort study conducted by Narayan et al. in 2021, which included patients who received and did not receive adjuvant/neoadjuvant chemotherapy and included 8864 patients, it was reported that PNI was a predictive marker for RFS.[17] Similarly, in our study, which included only patients receiving NAC, PNI provided the feature of being an independent predictive marker for both RFS and OS. Although its prognostic significance could not be demonstrated in the first studies in the literature, PNI was reported as prognostic in later studies, as in our study. This discrepancy may be caused by the difference in the methods used in the histopathological determination of PNI. In recent studies, the presence or absence of PNI is determined by using immunohistochemical methods unlike in the past.

There is no consensus in the literature about the prognostic feature of LVI. The prognostic significance of LVI could not be demonstrated in the studies of Ditsatam et al. and Fisher et al., which investigated the effect of LVI on survival in breast cancer patients.[28,29] However, in the studies of Ryu et al., Liu et al., and Hamy et al., which included patients receiving NAC only, LVI was reported as a prognostic marker for both RFS and OS.[6,23,30] Consistent with studies in which only patients re-

ceiving NAC were included, LVI was also found to be predictive in RFS and OS in our study. Since LVI lost its meaning in the multivariate analysis, it could not provide an ideal marker and was not found as an independent predictive marker.

In our study of survival association with HR+/Her2-, Her2+ and Triple negative subtypes based on HR and Her2 status of the primary tumor, PNI made a significant difference in survival in all subtypes for both RFS and OS. As far as we know, there is no study in the literature that includes the analysis of PNI according to breast cancer subtypes. In the study of Liu et al, which included breast cancer patients receiving NAC in the USA population, it reported LVI as significant for survival in both OS and RFS only in the triple-negative group, but not in other groups.[23] Similarly, in our study, there was a significant difference in survival distribution for both RFS and OS in the LVI triple negative group. Differently, it was found to be associated with RFS in the HR+/Her2- group.

The limitations of our study are that it was designed as a single-center and retrospective. The strengths of our analysis are that only patients receiving neoadjuvant chemotherapy are included, the same neoadjuvant treatment regimen is administered in a single institution, and pathological examinations of all patients are repeated by a different team of pathologists specializing in the evaluation of breast cancer tumors.

In conclusion, while LVI was not found to be an independent prognostic marker alone in breast cancer patients who received NAC and subsequently underwent surgery, we proved that PNI is a prognostic marker predicting RFS and OS. We found that the effects of LVI and PNI on survival differ according to breast cancer molecular subtypes. We suggest that PNI, which we have identified as a strong predictive marker, may be an important surrogate marker for RFS and OS in breast cancer, and may be a guide for identifying high-risk patients for relapse, and may even be included in new staging systems.

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