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Original Article

Perivascular Invasion: A Promising Prognostic Parameter for Breast Cancer

Perivasküler İnvazyon: Meme Kanserinde Umut Verici Prognostik Parametre

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ABSTRACT

Objective: Angiotropism/perivascular invasion (PVI) is an emerging topic in various types of cancer, with studies primarily focusing on melanoma. However, limited data are available on the significance of PVI in breast cancer. This study aimed to assess the prognostic significance of PVI in breast cancer and its correlation with traditional clinicopathological prognostic parameters.

Methods: A total of 150 patients with breast cancer diagnosed between July 2020 and January 2022 were included. Clinicopathological data were retrieved from the hospital records. The presence of PVI was evaluated on hematoxylin&eosin stained slides, and the association between PVI and clinicopathological parameters was statistically analyzed. A p-value of <0.05 was regarded as statistically significant.

Results: All patients were female. The mean age was 54.0±13.6 years (range 26-97 years). PVI was significantly more common in patients with ≥2.5 cm tumors and the absence of PVI showed a significant correlation with a lower histologic grade (p=0.004 and p=0.040, respectively). Lymphovascular invasion (LVI) and perineural invasion (PNI) were also significantly more frequent in tumors with PVI (p=0.001 and 0.02, respectively). There was a statistically significant association between the absence of both PVI and extranodal extension (ENE) (p=0.035).

Conclusions: The specific role of PVI in different types of cancer has not yet been clarified. Our findings showed that PVI was significantly associated with tumor size, histological grade, LVI, PNI, and ENE, all of which are well-known negative prognostic factors in breast cancer. The presence of PVI is a promising topic in breast cancer research, and the PVI status in pathology reports may help oncologists perform better risk assessments for patients with breast carcinoma.

Keywords: Breast, cancer, perivascular invasion, angiotropism, prognosis

ÖZ

Amaç: Anjiyotropizm/perivasküler invazyon (PVI), çeşitli kanser türlerinde yeni ortaya çıkan bir konudur ve çalışmalar çoğunlukla melanoma odaklanmaktadır. Ancak meme kanserinde PVI'nın önemi hakkında sınırlı miktarda veri bulunmaktadır. Bu çalışmada PVI'nın meme kanserinde prognostik önemini ve geleneksel klinikopatolojik prognostik parametrelerle ilişkisini değerlendirmeyi amaçladık.

Yöntemler: Temmuz 2020-Ocak 2022 tarihleri arasında meme kanseri tanısı alan toplam 150 hasta dahil edildi. Klinikopatolojik veriler hastane kayıtlarından elde edildi. Hematoksilen-eozin boyalı lamlarda PVI varlığı değerlendirildi ve PVI ile klinikopatolojik parametreler arasındaki ilişki istatistiksel olarak analiz edildi. İstatistiksel anlamlılık olarak p değerinin <0,05 olduğu kabul edildi.

Bulgular: Hastaların tamamı kadındı. Ortalama yaş 54.0±13,6 (dağılım 26-97) idi. PVI, 2,5 cm'den büyük tümörleri olan hastalarda anlamlı derecede daha yaygındı ve PVI yokluğu anlamlı derecede daha düşük histolojik derece ile ilişkiliydi (sırasıyla p=0,004 ve 0,040). Lenfovasküler invazyon (LVI) ve perinöral invazyon (PNI)da PVI'lı tümörlerde anlamlı olarak daha sık görüldü (sırasıyla p=0,001 ve 0,02). PVI ile ekstranodal uzanım (ENU) yokluğu arasında istatistiksel olarak anlamlı ilişki vardı (p=0,035).

Sonuçlar: PVI'nın çeşitli kanser tiplerindeki spesifik rolü henüz netleştirilmemiştir. Ancak bulgularımız, PVI'nın, meme kanserinde iyi bilinen negatif prognostik faktörler olan tümör boyutu, histolojik derece, LVI, PNI ve ENU ile anlamlı şekilde ilişkili olduğunu göstermektedir. Bu nedenle PVI varlığı meme kanseri açısından ümit verici bir konudur ve patoloji raporunda PVI durumunun yer alması onkoloğa meme karsinomu olan hastalarda daha iyi risk değerlendirmesi yapmada yardımcı olabilir.

Anahtar kelimeler: Meme, kanser, perivasküler invazyon, anjiyotropizm, prognoz

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INTRODUCTION

The passive spread of tumor cells through vascular structures is considered most common mechanism of metastasis in patients with cancer. Additionally, tumor cells can actively disseminate along neural structures and the abluminal surface of vascular spaces[1]. Pericytic angiotropism, also known as perivascular invasion (PVI), was first described in melanomas[2]. The term describes the movement of tumor cells along the external surface of blood vessels. Some studies have identified this mechanism as being associated with an elevated risk of local recurrence and metastasis in melanoma[3,4]. The concept of "PVI" is now being increasingly investigated in other tumors, including pancreatic and prostatic adenocarcinomas, well-differentiated liposarcomas, endometrial and tubo-ovarian carcinosarcomas, and sarcomatoid carcinoma of the vulva[5-8].

Breast cancer is the primary cause of cancer-related mortality in women[9]. When examining the relationship between PVI and breast cancer is poorly understood. A previous study reported that PVI was correlated with infiltrative tumor behavior and occult lymph node involvement in invasive lobular breast carcinoma[10]. Additionally, periarterial and perivenous invasion in invasive breast carcinoma of the no special type (NST) was significantly correlated with lymph node metastasis, as demonstrated in a study by Shioya et al[11].

Investigating the relationship between vascular structures and tumor cells, specifically cancerous invasion around vessels, could provide a new method for detecting LVI and linking it to lymph node metastases. Therefore, our study focused on detecting PVI in breast cancer and examining its association with key clinicopathological prognostic factors, as well as LVI and lymph node metastasis.

MATERIALS and METHODS

Ethical Approval

This retrospective study protocol and informed consent form were approved by the Clinical Research Ethics Committee of Başakşehir Çam and Sakura City Hospital (decision no: 8, date:31.03.2021). This study was conducted in compliance with the 2013 Declaration of Helsinki. Patients provided informed consent for the use of histopathological images. This study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[12].

Patient Selection

In total, 178 consecutive mastectomy specimens from patients who underwent breast cancer surgery were retrospectively evaluated in the Department of Pathology at our institution between July 2020 and January 2022. The assessment of the required sample size was based on the total patient population who received treatment in the defined period. Follow-up intervals were documented for the overall survival analysis. Twelve patients were lost to follow-up; therefore, phone calls were organized to collect missing follow-up data for these individuals.

Clinical Information and Histopathological Evaluation

The clinical and histopathological parameters, encompassing age, multifocality, tumor size, histologic type and grade, presence of LVI, presence of perineural invasion (PNI), tumor stage (pT), nodal status (pN), presence of extranodal extension (ENE), and receptor status [estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2) status, and Ki67 labeling index] through immunohistochemical staining), was retrieved from the hospital's digital medical record system and corresponding pathology reports.

Patients' ages were categorized into two groups: <50 years and ≥50 years old. Tumor sizes were grouped as <2.5 cm and ≥2.5 cm. The histological types were invasive carcinoma of NST, invasive lobular carcinoma, and others. Histologic grading was performed using the Nottingham histologic score, which was classified as Grade 1, 2, or 3[13]. The presence or absence of multifocality, LVI, PNI, and ENE was noted. The stages for pT and pN were determined based on both pathological reports and clinical information. pTs were classified into stages 1, 2, 3, and 4, whereas nodal stages (pN) were categorized as 0, 1, 2, or 3, in accordance with the guidelines established by the College of American Pathologists (CAP)[13].

Immunohistochemical assessment of ER, PgR, and HER2 was carried out in line with the CAP/American Society of Clinical Oncology (ASCO) Guidelines[13,14]. HER2 positivity was determined by the presence of complete and circumferential immunohistochemical expression in >10% of tumor cells. Equivocal HER2 positivity was further analyzed by silver-enhanced in situ hybridization in accordance with the ASCO/CAP guidelines[13]. The proportion of tumor cells positive for Ki67 was assessed in hot spots, with a cut-off value of 30% based on the latest international consensus study[15]. Tumors were classified into five molecular based on the St Gallen International Expert Consensus 2013: Luminal A (ER and PgR-positive, HER2-negative, and Ki67 ≤14%); luminal B1 (ER-positive,

HER2-negative, and either PgR<10% or negative or Ki67 >14%); luminal B2 (ER-positive, HER2-overexpressed or amplified, any PgR, any Ki67); HER2-positive (non-luminal) (HER2-overexpressed or amplified, ER-negative and PgR-negative) and triple-negative breast cancer (ER-negative and PgR-negative, HER2-negative)[16].

Evaluation of PVI

PVI was defined as tumor cells encircling the outer walls of blood vessels or lymphatics, within 1-2 mm of the leading edge of the primary tumor, as previously described[17]. The presence of PVI at the edges or periphery of the tumor was evaluated by using hematoxylin&eosin (H&E) staining alone. All tumor slides, including those stained with H&E, were reviewed for the presence of PVI.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (Chicago, IL). Distributional characteristics, numerical parametric data as mean±standard deviation, whereas median and interquartile range were used to describe non-parametric data. Categorical data are expressed as frequencies. The comparison of categorical variables was carried out using Pearson's chi-square test, Fisher's exact test, and the Freeman-Halton test. The t-test was used to analyze independent numerical variables with parametric data, whereas the Mann-Whitney U test was used for non-parametric data. A complete-case analysis strategy was used to address missing data. Multivariate logistic regression was applied to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between clinical and pathologic parameters and presence of PVI. Statistical significance was set at a p-value threshold of <0.05.

RESULTS

The study involved 150 patients in total. Twenty-eight patients who received neoadjuvant chemotherapy were excluded from the study. Sentinel lymph node dissection was performed in all patients, and axillary lymph node dissection was performed in 64 patients based on the results of frozen section analysis or clinical considerations.

The study included female patients with an average age of 54.0±13.6 years (range: 26-97 years). Among the patients, 66% (n=84) were ³50 years old. Tumors were multifocal in 27% (n=40) of the patients. The mean diameter of the tumor was 2.7±1.9 cm (ranging from 0.2 to 15 cm), and 54% (n=81) of the patients had a tumor diameter of <2.5 cm.

The most common histologic type was invasive carcinoma of NST (78%, n=117), followed by invasive lobular carcinoma (9%, n=13), and other histologic subtypes (13%, n=20) [apocrine carcinoma (n=1), mucinous carcinoma (n=5), tubular carcinoma (n=3), cribriform carcinoma (n=2), micropapillary carcinoma (n=1), solid papillary carcinoma with invasion (n=2), invasive carcinoma with mixed ductal and lobular features (n=6)].

Table 1. Demographic and clinicopathological characteristics of all patients.

		Patient count (n=150)
Age	<50 years old	66 (44%)
	³50 years old	84 (66%)
Multifocality	Present	40 (27%)
	Absent	110 (73%)
Tumor size	<2.5 cm	81 (54%)
	≥2.5 cm	69 (46%)
Histologic type	Invasive carcinoma of the NST	117 (78%)
	Invasive lobular carcinoma	13 (9%)
	Others	20 (13%)
Histologic grade	1	22 (15%)
	2	78 (52%)
	3	50 (33%)
Lymphovascular invasion	Present	73 (49%)
	Absent	77 (51%)
Perineural invasion	Present	56 (37%)
	Absent	91 (63%)
Tumor stage (pT)	1	53 (35%)
	2	79 (53%)
	3	10 (7%)
	4	8 (5%)
Nodal stage (pN)	0	75 (50%)
	1	53 (36%)
	2	11 (7%)
	3	11 (7%)
Extranodal extension	Present	50 (33%)
	Absent	100 (67%)
Molecular subtypes	Luminal A	34 (23%)
	Luminal B1	75 (50%)
	Luminal B2	23 (15%)
	HER2 (+) nonluminal	5 (3%)
	Triple negative	13 (9%)

NST: No special type, HER2: Human epidermal growth factor receptor 2

The most common histologic grade of the tumors was Grade 2 (52%, n=78). LVI was present in 49% (n=73) of the patients, whereas PNI was detected in 37% (n=56). Metastatic nodal disease (pN1, pN2, and pN3) was observed in 50% (n=75) of the patients. Among the molecular subtypes, the most common was the luminal B1 subtype, accounting for 50% (n=75) of the patients. The demographic and clinicopathological data for all patients are provided in Table 1.

PVI was detected in 30% (n=45) of the patients. Among these, PVI involved capillaries in 47% (n=21) of the patients, while 53% (n=24) showed involvement of medium- to large-caliber vessels. The histopathological appearance of PVI in invasive carcinoma of NST is shown in Figure 1.

PVI was significantly more common in patients with tumors ³2.5 cm (p=0.004). A significant statistical relationship was observed between the absence of PVI and histologic grade 1 tumors (p=0.040). Furthermore, the presence of LVI and PNI was significantly more common in tumors with PVI (p=0.001 and p=0.020, respectively).

The absence of PVI was significantly more common in tumors without ENE (p=0.035). No statistically significant correlation was observed between PVI and molecular subtypes (p>0.05). The results of the multivariate logistic regression analysis indicated that patients with LVI had a threefold higher risk of PVI (OR=3.226, 95% CI=1.308–7.957, p=0.011).

Table 2 presents the univariate and binary logistic regression analyses of clinicopathological parameters in relation to PVI status.

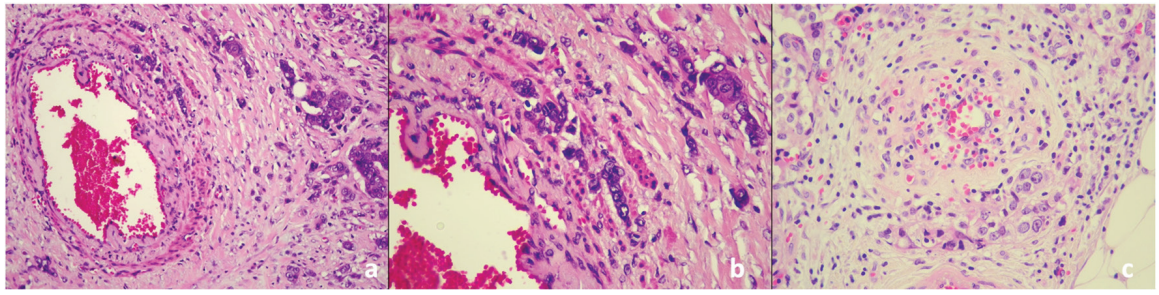

Figure 1. Perivascular invasion and infiltration of tumor cells surrounding vascular structures. a: Invasive carcinoma of no special type (H&E, x200), b: Invasive carcinoma of no special type (H&E, x400), c: Invasive carcinoma of no special type (H&E, x400).

H&E: Hematoxylin&eosin

Table 2. Univariate and binary logistic regression analyses of clinicopathological parameters according to perivascular invasion status.

Patient and tumor characteristics		Perivascular invasion		Univariate analysis	Binary logistic regression analysis	
		Present (n=45)	Absent (n=105)	p-value	p-value	Odds ratio
Tumor size (cm)	**<2.5**	16 (11%)	65 (43%)	**0.004[1]***	-	
	≥2.5	29 (19%)	40 (27%)			
Histologic grade	**1**	3 (2%)	19 (13%)	**0.040[2]***	0.443[3]	1.096
	2	30 (20%)	48 (32%)			
	3	12 (8%)	38 (25%)			
Lymphovascular invasion	**Present**	32 (21%)	41 (27%)	**0.001[1]***	**0.011[3]***	**3.226**
	Absent	13 (9%)	64 (43%)			
Perineural invasion	**Present**	23 (15%)	34 (23%)	**0.020[1]***	0.092[3]	0.471
	Absent	22 (15%)	71 (47%)			
Extranodal extension	**Present**	21 (14%)	29 (19%)	**0.035*[1]**	0.332[3]	0.645
	Absent	24 (16%)	76 (51%)			

*p< 0.05, [1]: Pearson's chi-square test, [2]: Fisher's freeman's Halton test, [3]: Binary logistic regression analysis.

Follow-up

The average follow-up time was 28.0±6.2 months, with a median of 27 months (ranging from 2 to 39 months) for overall survival. Eight patients died because of the disease. None of these patients had PVI; however, they presented with other negative prognostic indicators, including advanced histologic grade, later-stage tumor, LVI, and metastatic nodal disease.

DISCUSSION

This study examined the presence and prognostic value of PVI in patients with breast cancer. In addition to the strong association between PVI and LVI, we observed a correlation between PVI and other poor prognostic factors, including higher histological grade, PNI, and ENE. The main limitations of this study include the limited sample size and the short follow-up duration, which hindered a thorough survival analysis.

In our study, we observed that larger tumors more frequently exhibited PVI. This may be attributed to the irregular, infiltrative growth pattern, which is typical of larger malignant tumors. Igawa et al. recently reported that PVI was associated with infiltrative tumor growth in invasive lobular carcinoma of the breast[10]. Additionally, a study on gastric cancer found cancer cells in the periarterial tissues of patients with advanced gastric cancer patients[18].

In the current study, a significant relationship was observed between tumor grade and PVI. Although the majority of our patients had grade 2 tumors, PVI was significantly less common in those with lower grades. There are currently no studies in the literature that examined the relationship between PVI and tumor grade, and our findings contribute to the existing literature in this regard. While this observation warrants verification in larger study groups, it likely reflects the epithelial-to-mesenchymal transition process, as high-grade tumors tend to migrate more easily to perivascular areas due to the loss of adhesion molecules.

Shioya et al.[11] demonstrated that PVI could be highly sensitive and prevalent (95.5%) in invasive carcinoma of NST with lymph node metastases. In their study, the authors also reported that PVI was observed in 75.4% of tumors without lymph node metastasis. The authors concluded that lymphatic invasion could occur prior to lymph node metastasis. A study on PVI in invasive lobular carcinoma found that PVI is associated with lymph node metastasis in the absence of lymphadenopathy, which can be challenging to detect even with imaging techniques[10]. In light of the existing literature, our findings also suggest a strong relationship between PVI and LVI. We observed PVI in half of the patients with lymph node metastasis, which is consistent with the expectations based on prior research. However, our study did not support the hypothesis that PVI occurs before lymph node metastasis, as we found a PVI rate of only 13% in patients without lymph node metastasis, a rate lower than that reported in the literature.

PVI appears to be a consequence of talk between tumor cells and blood vessels, potentially representing an early phase of LVI, as the significant association between PVI and LVI persisted in multivariate analysis. However, further studies, particularly those using in vitro techniques, are necessary to test these theories.

In addition to LVI, PNI was found to be correlated with PVI. Fedda et al. reported PVI in a patient with recurrent acantholytic squamous cell carcinoma of the scalp, which was characterized by poor differentiation and significant PNI[19]. They stated that the concept of PVI is similar to that of PNI, which is consistent with our findings.

The association between ENE and poor prognosis in breast cancer has been demonstrated in various studies[20,21]. Although the data on this issue remain conflicting, most a negative prognostic effect of ENE in patients with breast cancer. We found that the absence of ENE was significantly associated with the absence of PVI. As far as we know, our study is the first to reveal this association, which may be particularly important for exploring different mechanisms of metastasis to lymph nodes. We believe this aspect warrants further investigation.

The molecular subtypes of breast cancer are an evolving topic that provides crucial insights into the mechanisms underlying the disease. Each tumor type has a distinct prognosis and various heterogeneous features[22]. In a recent study, patients with triple-negative breast cancer exhibited higher microvascular density; however, this finding did not directly support the presence of PVI[23]. In our study, PVI was not found to be specific to any molecular subtype of breast cancer, likely due to tumor heterogeneity.

Although the mechanism of PVI can be described as the movement of tumor cells along the abluminal side of blood vessels, there is a lack of standardized definitions for evaluating tumor cells associated with vessels with varying wall thicknesses[24]. PVI can affect capillaries and larger vessels. Although most blood vessels affected by PVI in melanoma are typically capillaries, carcinoma often involves medium- to large-caliber vessels[25,26]. In our

study of breast carcinomas, we observed slightly higher involvement of larger caliber vessels compared with capillaries.

CONCLUSION

In conclusion, our study provides new insights into the relationship between PVI and clinicopathological features of breast cancer. Our findings suggest that the presence of PVI may raise the suspicion for the existence of LVI and/or PNI in breast carcinomas, particularly in large or high-grade tumors. The incorporation of PVI status into pathology reports could enhance oncologists' understanding and improve prognostic predictions. Tumor spread is a critical concern in breast cancer, and we believe our findings contribute valuable insights into this important topic.

Ethics

Ethics Committee Approval: This retrospective study protocol and informed consent form were approved by the Clinical Research Ethics Committee of Başakşehir Çam and Sakura City Hospital (decision no: 8, date:31.03.2021).

Informed Consent: This study was conducted in compliance with the 2013 Declaration of Helsinki. Patients provided informed consent for the use of histopathological images.

Footnotes

Author Contributions

Surgical and Medical Practices: BÇ.G., T.S.A., H.E., E.Ş., B.P., Concept: BÇ.G., T.S.A., B.P., Design: BÇ.G., T.S.A., B.P., Data Collection and/or Processing: BÇ.G., T.S.A., H.E., H.İ.Ö., E.Ş., Analysis and/or Interpretation: BÇ.G., T.S.A., H.E., H.İ.Ö., Literature Search: BÇ.G., T.S.A., H.İ.Ö., B.P., Writing: BÇ.G., T.S.A., B.P.

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