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ORIGINAL ARTICLE

Lymphovascular infiltration in the tumor bed is a useful marker of biological behavior in breast cancer

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Summary

Purpose: *Tumor cells can metastasize by entering existing vessels or new vessels actively recruited into the primary tumor. Invasion of the lymphatics and blood vessels in the periphery of the tumor seems to be a prerequisite step in the metastatic process. The aim of this study was to correlate peripheral lymphatic vessel infiltration (PLI) and peripheral blood vessel infiltration (PVI) in a cohort of patients with invasive ductal carcinoma of the breast with various other prognostic parameters and outcome.*

Methods: *The study population consisted of 236 female patients with invasive ductal breast carcinomas, who had been operated between 2011 and 2013. The registered data included age at diagnosis, histological subtype, tumor size, TNM stage, histological grade, estrogen (ER) and progesterone receptors (PR), HER-2, p53, and PLI and PVI.*

Results: *Pathological examination revealed that 22.5% of the patients had PVI and 37.3% had PLI at the tumor front. PVI correlated with younger age ($p<0.05$), higher histologic grade ($p<0.05$), advanced TNM stage ($p<0.05$), higher T stage ($p<0.05$), higher N stage ($p<0.05$) and positive Ki67 expression ($p<0.05$). Similarly, PLI correlated with higher histologic grade ($p<0.05$), advanced TNM stage ($p<0.05$), higher T stage ($p<0.05$) and higher N stage ($p<0.05$). Statistical analysis did not reveal significant correlation between the presence of tumor blood and lymphatic vessels with infiltration in overall (OS) and disease-free survival (DFS).*

Conclusions: *PLI and PVI are important markers of worse clinical outcome as shown by their association with other established factors, but no association with recurrence and survival could be proven.*

Key words: *blood vessel infiltration, breast cancer, infiltrative breast cancer, lymphatic vessel infiltration, tumor front, tumor periphery*

Introduction

The lymphatic system is the primary pathway of metastasis from breast cancer, whereas lymph node metastasis is one of the most important prognostic factors for the patient's outcome. Lymphovascular invasion of tumor cells, which is dissemination of tumor cells into endothelium-lined lymphatic and/or blood vessels is a prerequisite for distant metastasis. Lymphatic vessels are considered as the main route of tumor cells to reach axillary lymph nodes [1].

Tumor cells can escape from the primary site by entering existing vessels or new vessels actively recruited into the primary tumor [2]. However, the relative importance of the established vessels vs the active invasion of a tumor by new blood and lymphatic vessels for the initial metastatic spread

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of tumor cells is still unclear. Lymphatic vessels were shown to be almost exclusively found at the tumor's invasion front and not within the tumor [3-6]. Additionally, lymph node metastases were shown to occur in tumors that lack intratumoral functional lymphatics, suggesting that functional lymphatics at the tumor margins are responsible for lymphatic dissemination [6]. On the other hand, angiogenesis is crucial for tumor growth, invasion, and haematogenous metastasis in breast cancer. However, there are definite biological differences between the ability of tumors to form intensive neovascularization and their ability to invade blood vessels. The growth of tumors is dependent on angiogenesis and the tumors' ability to metastasise is dependent on the access to the vasculature [7].

Routine assessment of PLI and LVI of tumor cells is now part of the minimum data set for breast cancer pathology report in a number of national pathology associations guidelines produced by the European Commission [8], the College of American Pathologists [9] and it is endorsed by the World Health Organization [10], and the American Joint Committee on Cancer/ International Union Against Cancer (AJCC/UICC) (7th Edn of TNM classification) as a prognostic factor in patients with breast cancer [11]. Emerging research on the importance of PLI in breast cancer was recognized by the St Gallen consensus conference in 2004, documenting PVI as a poor prognostic factor [12], but it has not been included in the National Institutes of Health guidelines [13].

The aim of this study was to correlate PLI and PVI in a cohort of patients with invasive ductal carcinoma with various other prognostic parameters and outcome.

Methods

The study population consisted of 236 female patients with invasive ductal breast carcinomas, with a mean age of 60 years old ±15.1 (SD) who had undergone surgery between 2011 and 2013 and had formalin-fixed paraffin-embedded blocks of the primary tumor available for further evaluation. The demographic, clinical and histopathological information of the patients were obtained from the Database of the Breast Unit of the First Department of Propaedeutic Surgery, Hippokrateion Hospital, Athens Medical School, University of Athens, Athens, Greece. The data included age at diagnosis, histological subtype, tumor size, histological grade (modified Bloom and Richardson), estrogen (ER) and progesterone receptor (PR) status and PLI and PVI. Patients were treated with either modified radical mastectomy or local tumor resection with axillary lymph node dissection followed by breast irradiation in some cases. Adjuvant chemotherapy and/or hormonal therapy were given based on hormone receptor status and pathological grade of the tumor.

Lymphovascular infiltration at the tumor front was requested as part of the routine pathological work-up at study entry and was evaluated with hematoxylin and eosin staining of sections of the tumor front. PVI was defined as the presence of tumor cell emboli within a vessel space, which were identified by the presence of blood filled spaces with endothelial cell lining. The study protocol required that at least two sections of primary tumor and adjacent benign peritumoral tissue be examined. PLI was shown by the presence of tumor cells in lymphatic channels. For this analysis, PVI and PLI were defined as 'present' or 'absent'.

Outcome data assessed included OS which was defined as the time from the date of diagnosis to either the date of last follow-up or death. DFS was defined as the time from the date of diagnosis till the date when presence of recurrent disease was first recorded.

Tumor blocks from each specimen were evaluated with immunohistochemical staining to assess ER, PR, p53, HER-2 and Ki-67 with monoclonal antibodies

Table 1. Tumor characteristics

Characteristics	*N (%)*
Tumor grade	
I	21(9.3)
II	98 (43.4)
III	107 (47.3)
T stage	
T1	51 (28.7)
T2	104 (58.4)
T3	14 (7.9)
T4	9 (5.1)
N stage	
N0	69 (44.2)
N1	65 (41.7)
N2	14 (9.0)
N3	8 (5.1)
TNM stage	
I	28 (18.2)
IIA	48 (31.2)
IIB	41 (26.6)
IIIA	20 (13.0)
IIIB	14 (9.1)
IV	3 (1.9)
Tumors positive for:	
ER	156 (72.6)
PR	138 (64.5)
HER2	124 (58.5)
EGFR	12 (16.0)
Ki67	44 (51.2)
p53	60 (75.9)
ER,PR,HER-2 negative tumors	19 (8.8)
Vascular vessel infiltration	53 (22.5)
Lymphatic vessel infiltration	62 (37.3)

ER: estrogen receptors, PR: progesterone receptors

Table 2. Relationships between vascular vessel infiltration and other clinicopathologic factors

Clinicopathologic factors	*Vascular vessel infiltration*		
	No (%)	*Yes (%)*	*p value*
Age, years±SD	61±14.3	54±16.2	<0.05
Grade			<0.05
I	11.9	0.0	
II	46.0	34.0	
III	42.0	66.0	
T stage			<0.05
T1	34.8	7.5	
T2	55.8	67.5	
T3	5.1	17.5	
T4	4.3	7.5	
N stage			<0.05
N0	52.9	16.2	
N1	32.8	70.3	
N2	10.9	2.7	
N3	3.4	10.8	
TNM stage			<0.05
I	24.3	0.0	
IIA	33.9	23.1	
IIB	20.9	43.6	
IIIA	13.0	12.8	
IIIB	7.8	12.8	
IV	0.0	7.7	
ER+	71.2	76.9	0.41
ER-	28.8	23.1	
PR+	64.8	63.5	0.85
PR-	35.2	36.5	
HER2+	61.3	50.0	0.15
HER2-	38.8	50.0	
ER/PR/HER-2 negative	8.6	9.6	0.82
Ki67 +	41.7	63.2	<0.05
Ki67 -	58.3	36.8	
p53 +	73.8	78.4	0.63
p53-	26.2	21.6	
EGFR +	9.8	23.5	0.10
EGFR -	90.2	76.5	

ER: estrogen receptors, PR: progesterone receptors

against the antigens ER (NCL-ER-6FII), PR (NCL-PGR), p53 (NCL-CMI) (Novocastra, UK), Ki67 (clone MIB1). The expression of HER-2 was evaluated with the HercepTest.

ER and PR were categorized as positive when the membrane staining was detected in more than 1% of tumor cells per field (x40).

p53 was categorized as positive when the membrane staining was detected in more than 10% of tumor cells per field (x40).

Ki67 index was characterized as qualitative variable, separating the study population into two groups of patients (with increased and decreased Ki67 index) using as separator the median threshold value of the Ki67 index (25%).

Statistics

All statistical analyzes were performed with the statistical package SPSS, version 13,00 (SPSS Inc, Chicago, IL). Quantitative variables were presented using means and standard deviations (mean±SD).The categorical variables were presented using the frequency (n) and the respective percentages (%). The survival curves were calculated by the method of Kaplan-Meier and differences were assessed using the log-rank test. Survival was further analyzed with multivariate Cox regression analysis which included the stage of disease. A p value <0.05 was determined as statistically significant.

Results

Pathological examination revealed that 22.5% of the patients had PVI and 37.3% had PLI at the invasive tumor front (Table 1).

Statistical analyses showed that PVI correlated with younger age (p<0.05), higher histologic grade (p<0.05), advanced TNM stage (p<0.05),

Table 3. Relationships between lymphatic vessel infiltration and other clinicopathologic factors

Clinicopathologic factors	*Lymphatic vessel infiltration*		
	No (%)	*Yes (%)*	*p value*
Age, years±SD	62±14.2	62±15.4	0.96
Grade			<0.05
I	13.3	1.7	
II	52.0	35.6	
III	34.7	62.7	
T stage			<0.05
T1	31.9	13.3	
T2	61.1	57.8	
T3	2.8	17.8	
T4	4.2	11.1	
N stage			<0.05
N0	55.6	10.8	
N1	36.5	43.2	
N2	6.3	27.0	
N3	1.6	18.9	
TNM stage			<0.05
I	19.0	2.6	
IIA	43.1	15.8	
IIB	24.1	23.7	
IIIA	6.9	31.6	
IIIB	6.9	23.7	
IV	0.0	2.6	
ER+	66.7	62.1	0.57
ER-	33.3	37.9	
PR+	58.1	55.2	0.72
PR-	41.9	44.8	
HER2+	59.5	72.4	0.11
HER2-	40.5	27.6	
ER/PR/HER-2 negative	9.2	13.8	0.38
Ki67 +	40.0	28.6	0.62
Ki67 -	60.0	71.4	
p53 +	33.3	57.1	0.49
p53-	66.7	42.9	
EGFR +	33.3	20.0	0.67
EGFR -	66.7	80.0	

ER: estrogen receptors, PR: progesterone receptors

higher T stage (p<0.05), higher N stage (p<0.05) and positive Ki67 expression (p<0.05; Table 2). In a similar manner PLI correlated with higher histologic grade (p<0.05), advanced TNM stage (p<0.05), higher T stage (p<0.05) and higher N stage (p<0.05; Table 3). Both PLI and PVI failed to correlate with the tumors' ER, PR, HER-2, and p53 status (Tables 2,3).

The median patient follow up was 30 months (range 22-46). During follow up 13.2% of the patients recurred and 6.5% died.

Statistical analysis did not reveal significant correlation between the presence of PVI and PLI in the OS and DFS (Figures 1-4).

Multivariate Cox regression analysis which included the lymph node involvement and the grade of differentiation showed that both PLI and PVI were not independent poor prognostic factors (Tables 4 and 5).

Discussion

Our results showed that PVI and PLI are important markers of high risk breast cancer through their association with other established risk factors. In breast cancer, the importance of PLI has been recognized more than four decades ago [14,15]. A significant amount of research has been published since then using a variety of indices to evaluate the PLI. While immunohistochemistry appears more reliable to detect PLI than hematoxylin & eosin, the optimal detection method remains unclear [16].

The results of the pathological examination of our cohort revealed that 22.5% of the patients had PVI and 37.3% had PLI at the invasive tumor front. Our results are consistent with the relevant literature whereas most previous studies on breast cancer reported occurrence of PLI in the

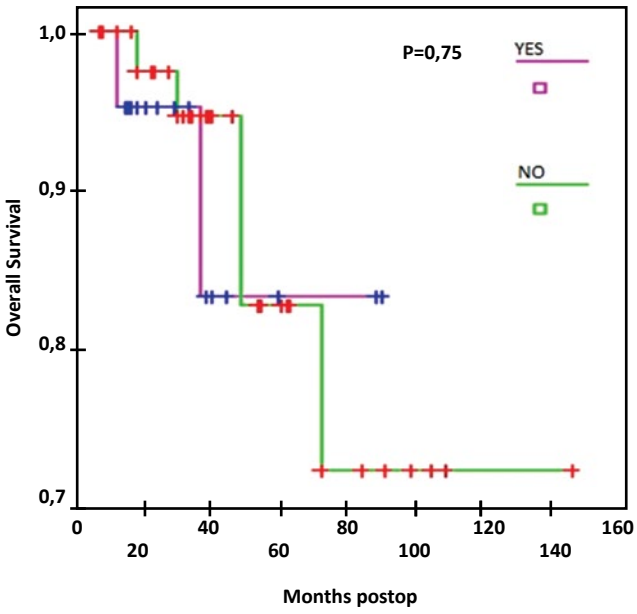

Figure 1. Kaplan-Meier curves of the association of PVI with overall survival (p=0.75).

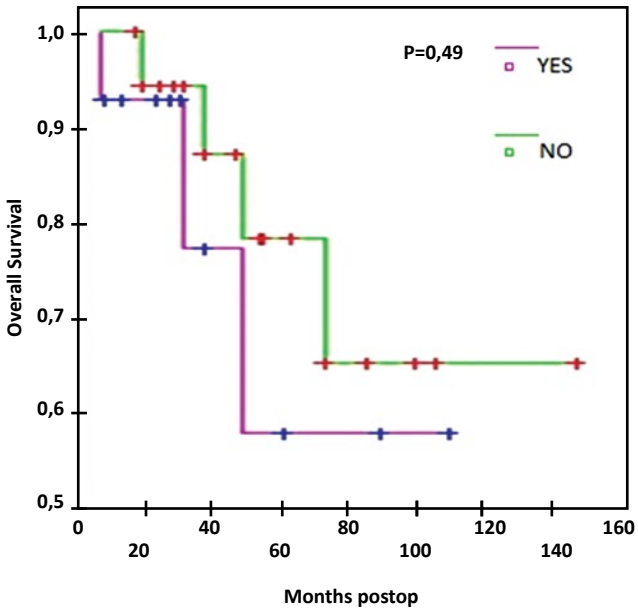

Figure 2. Kaplan-Meier curves of the association of PLI with overall survival (p=0.49).

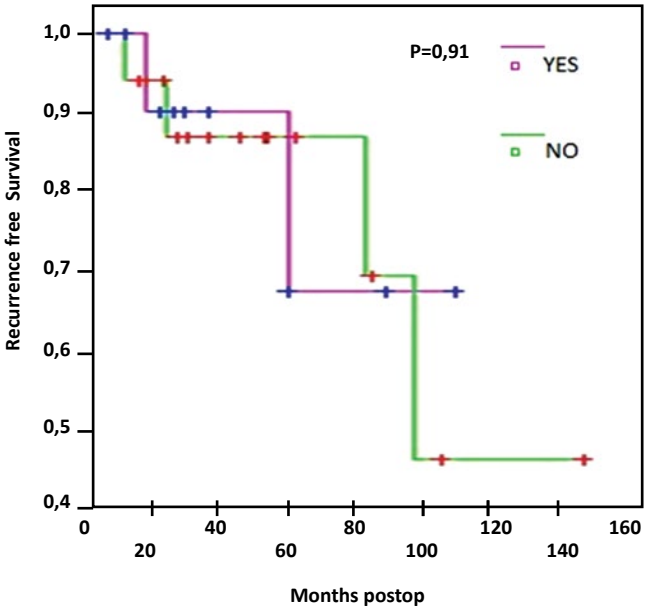

Figure 3. Kaplan-Meier curves of the association of PLI with disease-free survival (p=0.91).

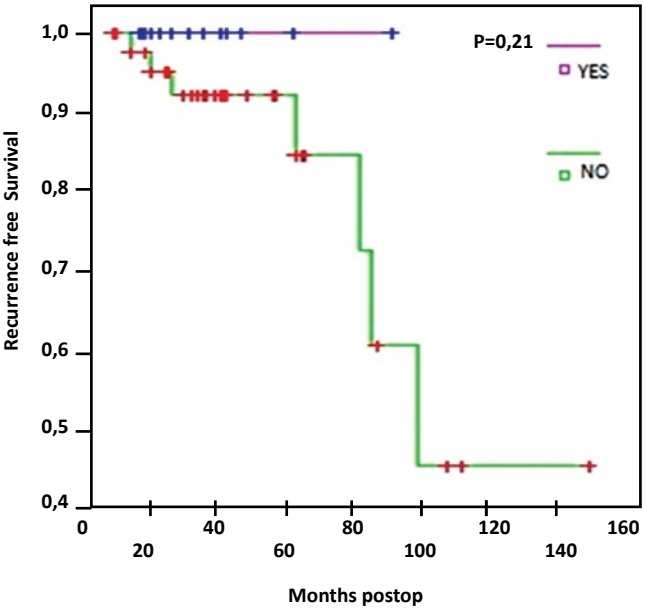

Figure 4. Kaplan-Meier curves of the association of PVI with disease-free survival (p=0.21).

range of 22-48% independent of stage, 15-28% range for patients with node negative tumor, and 24-45% for patients with triple-negative tumors [17]. Other reports documented LVI ranging from 25 to 35% for unselected population, 18-22% for lymph node-negative subgroup [18-21] and for those with pT1 tumors [22], and 45-60% for those with lymph node-positive tumors [23-25]. Studies that examined the PVI with the use of Factor VIII to identify the blood vessels reported occurrence from 16 to 27-29% in breast cancer patients and 10-18% in node-negative patients [26-28]. The results of the present study suggest that PVI is less frequent than PLI in breast cancer, consistent with previous studies [29,30]. This would suggest that PLI is potentially a more important route of breast cancer spread.

Statistical analysis of our data showed that LVI correlated with higher histologic grade, advanced TNM stage, higher T stage and higher N

Table 4. Multivariate analysis of prognostic factors by Cox proportional hazard model: disease-free survival

Factors	*p value*	*HR*	*95% CI*
Lymph node infiltration	<0.01	4.72	2.06-10.78
Histologic grade	0.06	0.50	0.24-1.05
PLI	0.44	1.61	0.47-5.43
PVI	0.34	1.75	0.54-5.67

For abbreviations see text

Table 5. Multivariate analysis of prognostic factors by Cox proportional hazard model: overall survival

Factors	*p value*	*HR*	*95% CI*
Lymph node infiltration	<0.01	6.31	1.79-22.28
Histologic grade	0.22	0.55	0.22-1.41
PLI	0.24	3.84	0.39-37.30
PVI	0.30	2.37	0.46-12.21

For abbreviations see text

stage. Most studies reported association of LVI with low histologic grade and this finding has been attributed to that fast-growing tumor produces more growth factors and offers a bigger clonal variety of tumor cells capable of invading lymphatic vessels compared with well-differentiated slow-growing tumors [32]. Two other studies [21,32] have demonstrated that the presence of LVI is associated with younger age, positive axillary lymph nodes, tumor size, and higher grade of malignancy. In these studies the proportion of patients with LVI has been small among patients with otherwise favorable characteristics.

We have not documented any correlation with the tumors' ER, PR, HER-2, and p53 status with both lymphatic and vascular vessel infiltration. Other authors have reported that breast cancer patients with LVI had statistically significant negative ER as well as larger tumors and of higher grade [33] . Studies performed by Tezuka et al. and Marinho et al. found that LVI was correlated with poorly grade, p-53 overexpression, high cell proliferation rate and negative hormone receptors' expression [34,35].

In a similar manner PVI correlated with younger age, higher histologic grade, advanced TNM stage, higher T stage, higher N stage and positive Ki67 expression. The association of PVI with age could be explained by the fact that young age is also an independent prognostic factor for women with breast cancer. Others have found in univariate analyses an association between the presence of PVI and higher tumor grade [36]. Among postmenopausal patients, the presence of PVI was also associated with larger tumor size. Other associations with clinical and pathological factors were not statistically significant [36].

We have found a strong association of PVI with lymph node status. Earlier work from the International Breast Cancer Study Group has shown similar findings and stated that the presence of vascular invasion predicts the presence of occult lymph node metastases on serial sectioning [37] and also predicts the presence of positive sentinel nodes [38]. Furthermore, the occurrence of PVI was significantly correlated with other prognostic features such as younger age, larger tumors, high histological grade, high Ki67, and HER-2 overexpression [36-38]. Others have also reported correlation between PVI and nodal involvement [39,40]. In fact, PVI is considered as a mirror of tumor cell dissemination to axillary lymph nodes and spread to distant sites [23].

LVI has also been shown to be a predictor of axillary lymph node metastasis [30,42,43]. Based on these reports, it has been proposed that LVI could be used to identify a subgroup of axillary node-negative patients with an unfavorable prognosis that are likely to benefit from adjuvant chemotherapy [12].

The results of the present study did not reveal any significant correlation between the presence of tumor infiltration of blood and lymphatic vessels in the tumor periphery and OS and DFS. A number of independent studies have investigated the prognostic value of LVI in node-negative and node-positive breast cancer [44-48]. The biggest study's results, which examined the prognostic influence of LVI in a prospectively identified cohort of more than 15000 breast cancer patients, reported statistically significant evidence for heterogeneity in the association between LVI and OS according to risk group in that LVI was associated with worse OS in the high-risk group but not in the low-risk group. Based on their findings the authors concluded that LVI seems to be a marker of poor prognosis among patients with early-stage breast cancer [33]. Colleoni et al. [21] found that extensive LVI was associated with a worse prognosis as compared with absence of LVI. However, their analysis was restricted to lymph node–negative patients, Several other independent studies using both H&E and immunohistochemistry methods have demonstrated a clear relationship between LVI and outcome in patients with negative lymph node status [13-15,19,23,32,40], and, with some controversy, in patients with positive

lymph node status [14,15].

In conclusion our data show that PVI and LVI are important markers of worse clinical outcome as is shown by their association with other established factors but no association with recurrence and survival could be noted. The discrepancy of the latter finding may be attributed to the unselected patients of our cohort.

Conflict of interests

The authors declare no confict of interests.

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