Comparison Between Invasive Breast Cancer With Extensive Peritumoral Vascular Invasion and Inflammatory Breast Carcinoma

A Clinicopathologic Study of 161 Cases

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ABSTRACT

Objectives: *Extensive peritumoral neoplastic lymphovascular invasion (ePVI) is a marker of aggressiveness in invasive breast carcinoma (BC).*

Methods: *We explored the impact of ePVI on different BC subtypes. In a total of 2,116 BCs, 91 ePVI-BCs, 70 inflammatory breast carcinomas (IBCs), and 114 casual BCs as a control group (CG-BC) were recruited.*

Results: *Patients affected by ePVI-BC were younger, had larger tumors, higher histologic grade, elevated Ki-67 score, Her2/neu overexpressed, and more lymph node metastases compared with CG-BC (*$P < .001$*). Interestingly, only younger mean age at diagnosis differentiated patients with ePVI-BC from patients affected by IBC. ePVI-BC showed a clinical outcome intermediate between the prognoses of IBC and CG-BC.*

Conclusions: *Results suggest that ePVI-BC and IBC may share some pathologic processes, providing a novel perspective on the heterogeneity of BC. Epidemiologic data and molecular studies on gene expression features are needed to rationally classify these tumors into their identified subtypes.*

Appropriate identification of prognostic factors and parameters predictive of responsiveness to specific treatment programs represents a major challenge in breast oncology. Conventional prognostic factors of survival, such as tumor size, lymph node status, and histologic grade, remain the most important determinants of 10-year survival for patients with breast cancer.[1-10] Nevertheless, most studies agree on the value of other factors, such as peritumoral lymphovascular invasion (PVI), for prediction of long-term survival.[11-26] Inflammatory breast carcinoma (IBC), the most aggressive manifestation of primary breast carcinoma, is characterized by poor prognosis compared with primary noninflammatory breast cancer.[27] IBC shows extensive PVI (ePVI), which is visible as multiple, and sometimes uncountable, tumor emboli.[28] However, ePVI is detected at a variable rate (5%-15%) in non-IBC breast cancer.[29] The weight of cumulative evidence suggests that the presence of ePVI in this subset of breast cancers is indicative of an unfavorable prognosis,[15,16,19,20,26,30] even in node-negative patients treated with either breast conservation therapy or mastectomy.[12,14,21,26,30-33] Accordingly, ePVI has been incorporated as a prognostic factor into numerous guidelines for adjuvant treatment in node-negative breast cancer.[32-36]

In the present study, we analyzed the clinical and biological characteristics of primary breast cancer with extensive vascular invasion in comparison with IBC.

Materials and Methods

Patients

A total of 2,116 consecutive patients affected by IBC were collected between January 1992 and December 2006 and included in the database of the Department of Pathology of the G.B. Rossi Hospital in Verona, Italy. Data on the patient's medical history, surgery, pathologic evaluation, and results of staging procedures (bone scan, chest film, and upper abdominal ultrasound examination) were evaluated. Specimens removed through surgical biopsy or mastectomy were retrospectively reviewed by breast pathologists (E.M. and A.R.). Pathologic assessment included the primary tumor size, histologic type, histologic grade, and axillary lymph nodes status.

Clinical and/or histopathologic criteria were adopted to include a patient in the IBC group. A histopathologic diagnosis of IBC was made when neoplastic emboli were observed within dermal lymphatic spaces.[28] Clinical evidence of IBC consisted of diffuse erythema, peau d'orange, edema, warmth, tenderness, breast enlargement, and diffuse induration of the breast on palpation, as described by Haagensen.[37]

In the current study, only strict morphologic criteria were adopted to define the phenomenon of lymphovascular invasion (LVI) by tumor cells. On morphology, endovascular neoplastic emboli were considered "true" only when neoplastic cells were in channel spaces lined by endothelial cells **Image 1**; all other spaces without certain peripheral endothelium were considered LVI mimickers **Image 2**. No qualitative distinction, "lymphatic," "venous," or "arterial" invasion, or immunohistochemical staining were applied. Immunohistochemical staining for lymphatic and venous channels using D2-40 and CD31, respectively, have been proposed to solve the problem concerning the retraction artifacts and for determining the type of lining endothelium.[38,39] Although immunostains may be helpful in confirming LVI, problems related to cross-reactivity and false-negative immunostaining for lymphatic endothelia have not been completely overcome,[38] and the adoption of strict morphologic criteria with conventional H&E stain for LVI remain of clinical value in identifying high-risk patients.[39]

The presence of neoplastic emboli in the lumen of peritumoral lymphovascular spaces, evaluable in more than one tumor block on H&E-stained slides, poised at more than one high power microscopic field away from the boundaries of the main tumor[30] and visible in more than 10 vascular spaces[40] was consistent with a diagnosis of IBC with ePVI (ePVI-BC).

A casual subset of patients affected by primary IBC without histologic criteria of IBC and ePVI-BC represented the control group-BC. Patients included in the control group were casually recruited among the first 10 consecutive breast cancer cases diagnosed each year between 1992 and 2006.

Estrogen receptor (ER) and progesterone receptor (PR) status; Ki-67 labeling index (Ki-67), as assessed with MIB1 monoclonal antibodies; and Her2/neu overexpression (HER2) were evaluated immunohistochemically on formalin-fixed, paraffin-embedded tissue blocks. ER and PR status was recorded as positive when nuclear staining was identified in more than 5% of neoplastic cells. Ki-67 labeling index was stratified as low when the Ki-67 staining score was 1% to

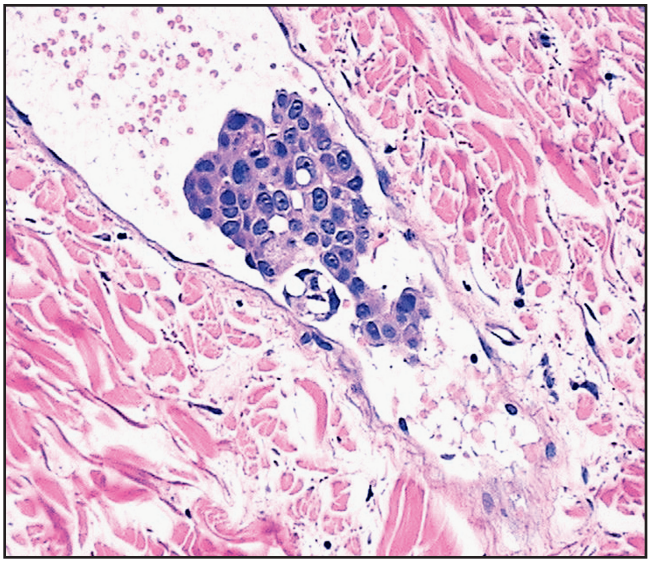

Image 1 Lymphovascular channel with the lumen partially occupied by an aggregate of tumor cells; note the inner channel wall lined by flattened endothelial cells (H&E, ×60).

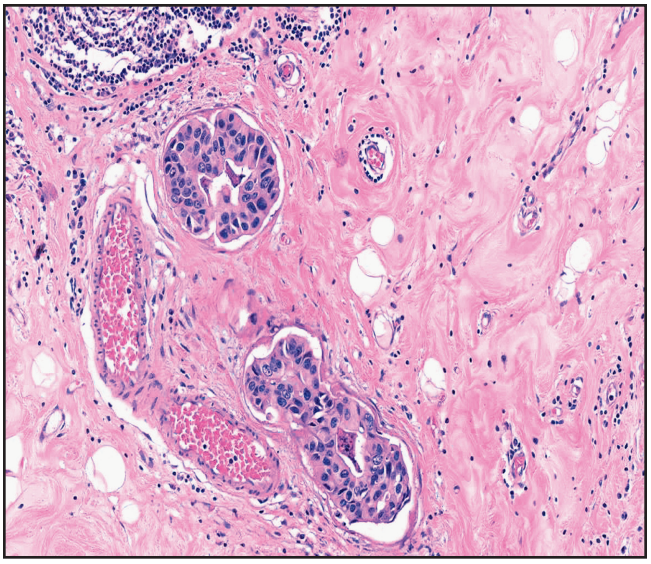

Image 2 Lymphovascular invasion mimicker. Artifactual retraction of stroma around tumor cells. The contour of tumor cell aggregate conforms exactly to the shape of the space in which it lies (H&E, ×40).

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10% of neoplastic cells, medium with 11% to 25%, and high with more than 25% of neoplastic cells. HER2 was graded from no staining (0) to weak (1+), moderate (2+), and intense membrane staining (3+) in more than 10% of tumor cells in the tissue section, according to HER2 testing guidelines of the American Society of Clinical Oncology and College of American Pathologists.[41] A score of 2+ was used as the cutoff point for fluorescence in situ analysis.

The clinical files were examined for treatment received by patients as systemic adjuvant therapy and surgical treatment.

Statistical Analysis

The Fisher exact and χ^2 tests were used to assess the association between categorical and ordinal variables in the three different groups of invasive cancer (IBC, ePVI-BC, and control group-BC). Disease-free survival (DFS) was defined as the length of time from the date of surgery and any relapse, the appearance of a second primary cancer, death, or the date of last follow-up visit. Overall survival (OS) was determined as the time of surgery to the date of death from any cause, or the date of the last follow-up visit. Survival plots according to age were drawn using the Kaplan-Meier method. All analyses were performed with STATA 13 (StataCorp, College Station, TX). A *P* value less than .05 was considered statistically significant.

Results

Clinicopathologic Parameters Differentiate Breast Cancer Subgroups

All patients with primary IBC (n = 70) and ePVI-BC (n = 91) recruited between January 1992 and December 2006 were eligible for the current study. The control group was originally composed of 140 patients; 26 cases were subsequently excluded because of in situ carcinoma, and thus 114 patients were included in the control group-BC category. The incident cancer rate distribution according to age and patient group was described by different curves **Figure 1**. The clinical data of patients and histologic characteristics of breast cancer subgroups considered for the analysis are shown in **Table 1**. We found that patients affected by ePVI-BC were more likely to be younger, to have a larger tumor with higher histologic grade, elevated Ki-67 score, HER2 overexpression, and positive axillary lymph nodes compared with patients in control group-BC ($P < .001$). The younger mean age at diagnosis differentiated patients with ePVI-BC from patients affected by IBC and control group-BC **Figure 2**. The higher number of metastatic axillary lymph nodes ($P = .006$) was the only statistically significant variable that differentiated IBC from ePVI-BC (Table 1). IBC subgroup differed significantly from control group-BC with regard to larger tumor size, higher histologic grade, and number of metastatic lymph nodes. In addition, IBC presented a higher rate of Her2/neu positivity and elevated Ki-67, ER, and PR compared with control group-BC. We also observed that both ER and PR positivity were inversely correlated with Ki-67 in the IBC subgroup ($P < .05$; Table 1). These data suggest that clinical and histopathologic features of IBC and ePVI-BC are significantly different when compared with control group-BC. Notably only two variables, age at diagnosis and the number of metastatic lymph nodes, differentiated IBC from ePVI-BC, thus reflecting a possible overlap between these two subgroups.

Differential Prognostic Value Among Breast Cancer Subgroups

We assessed whether subtypes differ in survival, as a general read-out of clinicopathologic significance. The mean

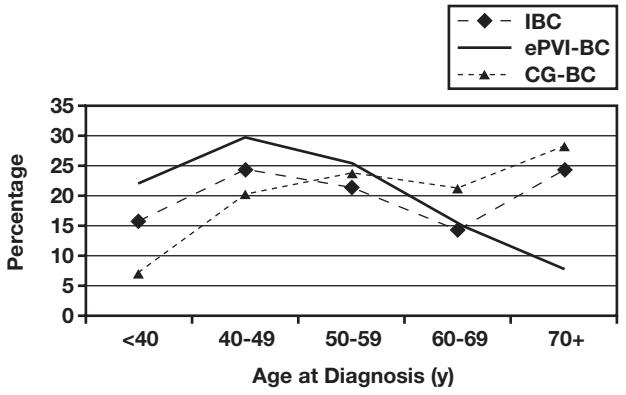

Figure 1 Percentage of patients according to cancer group and age. CG-BC, control group breast cancer; ePVI-BC, breast cancer with extensive peritumoral vascular invasion; IBC, inflammatory breast carcinoma.

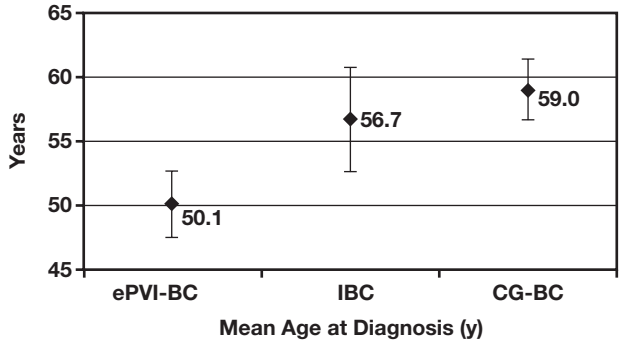

Figure 2 Cartesian diagram of mean patient age at diagnosis according to cancer group. CG-BC, control group breast cancer; ePVI-BC, breast cancer with extensive peritumoral vascular invasion; IBC, inflammatory breast carcinoma.

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Table 1
Characteristics of Patients According to Histologic Diagnosis and Therapy

Characteristics	IBC, No. (%)	ePVI-BC, No. (%)	CG-BC, No. (%)	*P* Value		
				ePVI-BC vs IBC	ePVI-BC vs CG-BC	IBC vs CG-BC
No. of patients	70	91	114			
Age group, y						
<40	11 (15.7)	20 (22.0)	8 (7.00)			
40-49	17 (24.3)	27 (29.7)	23 (20.2)			
50-59	15 (21.4)	23 (25.3)	27 (23.7)			
60-69	10 (14.3)	14 (15.4)	24 (21.1)			
70+	17 (24.3)	7 (7.70)	32 (28.1)	.06	<.001	.3
Tumor size						
>0.1-≤2 cm	14 (26.4)	39 (42.9)	88 (77.9)			
>2-≤5 cm	31 (58.5)	41 (45.1)	23 (20.4)			
>5 cm	8 (15.1)	11 (12.1)	2 (1.80)	.14	<.001	<.001
Total	53	91	113			
Unknown	17	0	1			
Tumor grade						
G1	2 (3.70)	1 (1.10)	30 (28.8)			
G2	15 (27.8)	23 (26.4)	51 (49.0)			
G3	37 (68.5)	63 (72.4)	23 (22.1)	.57	<.001	<.001
Total	54	87	104			
Unknown	16	4	10			
pN						
N+	49 (87.5)	68 (80.0)	26 (26.3)			
N–	7 (12.5)	17 (20.0)	73 (73.7)	.25	<.001	<.001
N0	7 (12.5)	17 (20.0)	73 (73.7)			
N1 (1-3)	12 (21.4)	34 (40.0)	19 (19.2)			
N2 (4-9)	13 (23.2)	19 (22.4)	7 (7.10)			
N3 (>10)	24 (42.9)	15 (17.6)	0 (0)	.006	<.001	<.001
Total	56	85	99			
Unknown	14	6	15			
ER status						
Positive	36 (58.1)	66 (72.5)	93 (84.5)			
Negative	26 (41.9)	25 (27.5)	17 (15.5)	.06	.04	<.001
Total	62	91	110			
Unknown	8	0	4			
PR Status						
Positive	26 (49.1)	55 (60.4)	85 (84.2)			
Negative	27 (50.9)	36 (39.6)	16 (15.8)	.2	<.001	<.001
Total	53	91	101			
Unknown	17	0	13			
Proliferative fraction						
1%-10%	31 (45.6)	36 (40.4)	78 (71.6)			
11%-25%	15 (22.1)	28 (31.5)	17 (15.6)			
>25%	22 (32.4)	25 (28.1)	14 (12.8)	.42	<.001	.001
Total	68	89	109			
Unknown	2	2	5			
Her2/neu status						
Not overexpressed	43 (64.2)	44 (51.8)	92 (89.3)			
Overexpressed	24 (35.8)	41 (48.2)	11 (10.7)			
Total	67	85	103	.17	<.0001	.0001
Unknown	3	6	11			
Adjuvant therapy						
ET	9 (15.0)	9 (13.6)	50 (62.5)			
CT	27 (45.0)	26 (39.4)	14 (17.5)			
ET + CT	24 (40.0)	31 (47.0)	16 (20.0)	.73	<.0001	<.0001
None	0	0	3 (2.60)			
Total	60	66	83			
Unknown	10	25	31			

CG-BC, control group breast cancer; CT, chemotherapy; ePVI-BC, breast cancer with extensive peritumoral vascular invasion; ER, estrogen receptor; ET, endocrine therapy; IBC, inflammatory breast carcinoma; pN, pathologic node; PR, progesterone receptor.

± standard deviation (SD) follow-up was 8.2 ± 4.1 years for patients in the control group-BC, 5.8 ± 3.4 years for patients with ePVI-BC, and 4.6 ± 3.2 years for patients with IBC. We then tested the association of each group with prognoses taking into account the differences in mean years of DFS and OS. The results indicate statistically significant differences for patients affected by ePVI-BC and IBC compared with the control group-BC **Figure 3**, **Figure 4**. Specifically, the

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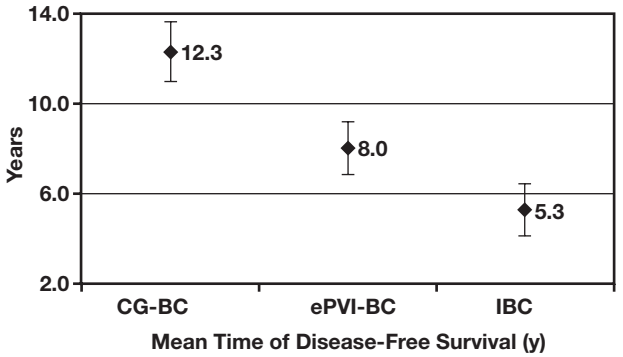

Figure 3 Cartesian diagram of mean time of disease free survival (DFS) by disease group expressed in years. Mean DFS times were as follows: control group breast cancer (CG-BC) group—12.3 years (95% confidence interval [CI], 10.9-13.6); breast cancer with extensive peritumoral vascular invasion (ePVI-BC) group—8.0 years (95% CI, 6.8-9.2); and inflammatory breast carcinoma (IBC) group—5.3 years (95% CI, 4.1-6.4).

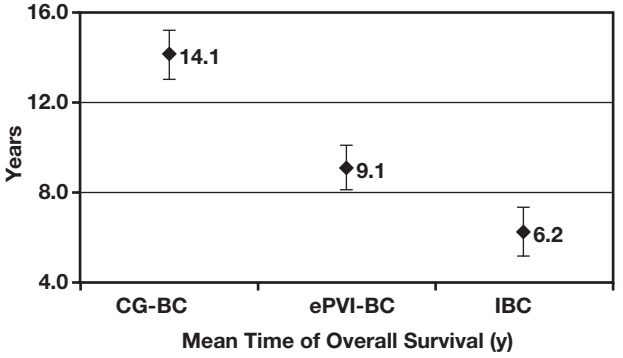

Figure 4 Cartesian diagram of mean time of overall survival (OS) by disease group expressed in years. Mean OS times were as follows: control group breast cancer (CG-BC) group—14.1 years (95% confidence interval [CI], 13.6-15.21); breast cancer with extensive peritumoral vascular invasion (ePVI-BC) group—9.1 years (95% CI, 8.1-10.1); and inflammatory breast carcinoma (IBC) group—6.2 years (95% CI, 5.17-7.32).

estimated proportion of surviving patients at 2 and 5 years was 80% and 51%, respectively, for IBC patients, 89% and 72%, respectively, for ePVI-BC patients, and 98% and 91%, respectively, for CG-BC patients. The DFS at 2 years was 61% for IBC, 81% for ePVI-BC, and 92% for control group-BC. The DFS at 5 years was 41% for IBC, 58% for ePVI-BC, and 78% for control group-BC.

The Kaplan-Meier curves for DFS and OS of the three groups are shown in **Figure 5** and **Figure 6**, respectively. Notably, IBC had poorer prognosis than ePVI-BC and control group-BC patients for both end points at 2 and 5 years. The ePVI-BC subgroup, however, preserved an intermediate clinical outcome between the poorer prognosis of IBC and the better prognosis of CG-BC. Altogether, these data suggest that IBC is associated with an adverse prognosis and that ePVI-BC patients present clinical and pathologic characteristics intermediate between IBC and control group-BC.

Discussion

In the present study, breast cancers with extensive peritumoral vascular invasion had biological characteristics that connote clinical aggressiveness.[12,35] The occurrence of ePVI was significantly correlated with unfavorable prognostic features such as young age at diagnosis,[42,43] large tumor size,[26] high histologic grade,[12,44,45] high Ki-67 labeling index, and Her2/neu overexpression[46] when compared with the control group cancer series (Table 1). In our series, 80% of ePVI-BC patients had axillary nodes metastases at onset, and 40% had four or more involved nodes (Table 1). The presence of axillary nodal metastases is the most powerful, independent prognostic parameter in women with primary breast cancer, and the number of involved lymph nodes is pivotal in risk evaluation to provide therapeutic guidance.[36] The correlation between lymphovascular invasion and the extent of nodal involvement has been reported,[25,38,47] and the association of tumor size and peritumoral vascular invasion has emerged as the most powerful independent predictor of sentinel lymph node metastasis.[25] Lymphovascular invasion is considered to be a reflection of tumoral cell dissemination to axillary nodes and distant sites,[48] and ePVI by itself has been associated with a 5.3-fold greater risk for sentinel lymph node involvement. Lauria et al[20] reported that the risk of death in a subgroup of node-negative IBC was more than two times higher in the presence of lymphovascular invasion. Based on this finding, it is reasonable to assume that ePVI-BCs are biologically more aggressive than breast cancers without vascular invasion.

In our series, no statistically significant differences emerged from a comparison of the clinicopathologic features of ePVI-BC and IBC, except for the distribution of patients in different pathologic node (pN) categories and the age of patients at the onset of disease (Table 1). In fact, while the node-negative patient rate was quite similar in the ePVI-BC and IBC groups, among node-positive cases, the highest proportion of ePVI-BC patients was pN1 (40%), and the largest percentage of IBC patients was allocated to the pN3 group (42.9%) (P = .006). In control group-BC patients, the distribution of clinical and pathologic variables was significantly different from both ePVI-BC and IBC, with a selective allocation of the highest proportion of patients to the class of variables associated with better prognosis (Table 1).

In the current study, the distribution of the age-specific incidence rates of breast cancer stratified in the three patient

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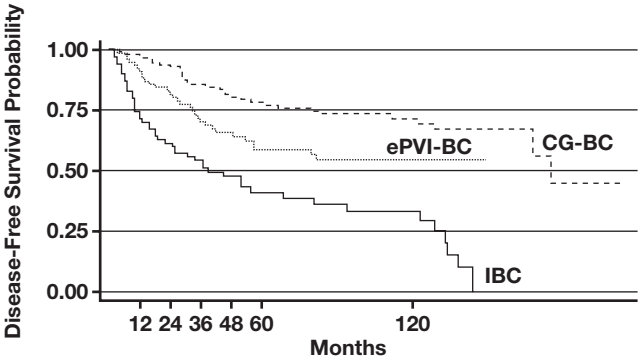

Figure 5 Kaplan-Meier representation of disease-free survival rates by disease group. Control group breast cancer (CG-BC) group vs breast cancer with extensive peritumoral vascular invasion (ePVI-BC) group, $P = .012$; ePVI-BC vs inflammatory breast carcinoma (IBC), $P < .001$; IBC vs CG-BC, $P < .001$.

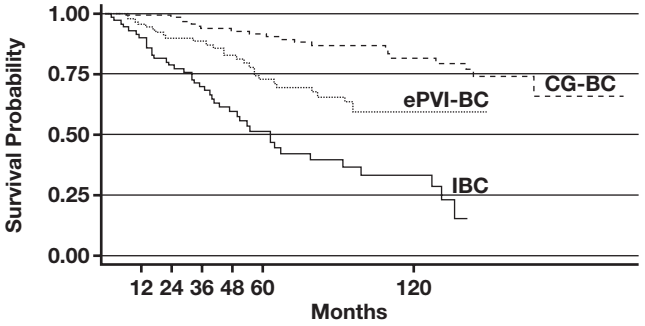

Figure 6 Kaplan-Meier representation of overall survival by disease group. Control group breast cancer (CG-BC) group vs breast cancer with extensive peritumoral vascular invasion (ePVI-BC) group, $P = .001$; ePVI-BC vs inflammatory breast carcinoma (IBC), $P < .001$; IBC vs CG-BC, $P < .001$.

groups was represented by different curves (Figure 1). The ePVI-BC age-specific incidence rate curve showed a single peak at age 40 to 49 years (median age at diagnosis, 50.1 years). IBC and control group-BC showed a bimodal incident rate distribution according to age. Our results on IBC and control group-BC are concordant with a large series from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute in which the bimodal age-specific incidence rate distribution was described for all cancer types, except medullary carcinoma.[49,50] In the SEER series, no data were provided on vascular invasion. However, these results allow speculation that there are different types of cancer groups in which the distribution of patients according to mean age at diagnosis, lymph node status, and cancer group suggests that the clinical behavior of ePVI-BC is similar to cancers that share several prognostic and predictive parameters of aggressive IBC (tumor size, grading, receptor status, Her2/neu status), but with clinical signs of a lower degree of progression (fewer positive nodes and a younger age at onset).

In our series, the results on DFS and OS rates at 2 and 5 years provided substantial additional evidence to support this hypothesis. Differences in terms of OS among ePVI-BC, IBC, and the control group were statistically significant ($P = .001$; Figure 6). Moreover, the clinical aggressiveness of IBC[27] was confirmed by our data, and the estimated proportion of surviving patients at 2 (80%) and 5 years (51%) was lower than ePVI-BC (89% and 72%, respectively) and control group-BC patients (98% and 91%, respectively). These data, coupled with the Kaplan-Meier curves for OS (Figure 6) and the distribution of mean years of survival on a Cartesian diagram (Figure 4), showed that ePVI-BC was positioned in an intermediate interval between IBC and control cancers. Similar results were obtained for DFS. Indeed, the Kaplan-Meier curves for DFS (Figure 5) and the Cartesian distribution diagram of mean years of DFS (Figure 3) showed that ePVI-BC patients had a prognosis intermediate between IBC and control group-BC.

In conclusion, breast cancers with massive vascular neoplastic emboli, associated or not with a clinical sign of inflammatory carcinoma, are highly aggressive diseases. To our knowledge, this is the first study to analyze breast cancer with extensive vascular invasion in comparison with inflammatory breast cancer, and showing that ePVI-BCs have more clinicopathologic affinity than differences with the most aggressive cancer in the breast. Our results could suggest that there is a biological link between diseases, but future studies are necessary to search for a molecular signature of these aggressive cancers.

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References

1. Say CC, Donegan WL. Invasive carcinoma of the breast: prognostic significance of tumor size and involved axillary lymph nodes. *Cancer*. 1974;34:468-471.
2. Rosen PP, Groshen S, Saigo PE, et al. Pathological prognostic factors in stage I (T1N0M0) and stage II (T1N1M0) breast carcinoma: a study of 644 patients with a median follow-up of 18 years. *J Clin Oncol*. 1980;7:1239-1251.
3. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer*. 1989;63:181-187.

DOI: 10.1309/AJCPOXKX67KRAOVM

4. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer: the value of histological grade in breast cancer: experience from a large study with long term follow-up. *Histopathology.* 1991;19:403-410.
5. Silverstein MJ, Gierson ED, Waisman JR, et al. Predicting axillary node positivity in patients with invasive carcinoma of the breast using a combination of T category and palpability. *J Am Coll Surg.* 1995;180:700-704.
6. Barth A, Craig PH, Silverstein MJ. Predictors of axillary node metastases in patients with T1 breast carcinoma. *Cancer.* 1997; 79:1918-1922.
7. Gann PH, Colilla SA, Gapstur SM, et al. Factors associated with axillary lymph node metastasis from breast carcinoma. *Cancer.* 1999;220:692-696.
8. Tabar L, Duffy SW, Vitak B, et al. The natural history of breast carcinoma: what have we learnt from screening? *Cancer.* 1999;86:449-462.
9. Chua B, Ung O, Taylor R, et al. Frequency and predictors of axillary lymph node metastases in invasive breast cancer. *ANZ Surg.* 2001;71:723-728.
10. Silverstein MJ, Skinner KA, Lomis TJ. Predicting axillary nodal positivity in 2282 patients with breast carcinoma. *World J Surg.* 2001; 25:767-772.
11. Nime FA, Rosen PP, Thaler HT, et al. Prognostic significance of tumor emboli in intramammary lymphatics in patients with mammary carcinoma. *Am J Surg Pathol.* 1997;1:25-30.
12. Rosen PP, Saigo PE, Braun DW Jr, et al. Predictors of recurrence in stage I (T1N0M0) breast carcinoma. *Ann Surg.* 1981;193:15-25.
13. Rosen PP, Saigo PE, Braun DW Jr, et al. Occult axillary lymph node metastases from breast cancers with intramammary lymphatic tumor emboli. *Am J Surg Pathol.* 1982;6:639-641.
14. Roses DF, Bell DA, Flotte TJ, et al. Pathologic predictors of recurrence in stage I (T1N0M0) breast cancer. *Am J Clin Pathol.* 1982;78:817-820.
15. Weigand RA, Isenberg WM, Russo J, et al. Blood vessel invasion and axillary lymph node involvement as prognostic indicators for human breast cancer. *Cancer.* 1982;50:962-969.
16. Davis BW, Gelber R, Goldhirsch A, et al. Prognostic significance of peritumoral vascular invasion in clinical trial of adjuvant therapy for breast cancer with axillary lymph node metastasis. *Hum Pathol.* 1985;16:1212-1218.
17. Lee AK, DeLellis RA, Silverman ML, et al. Prognostic significance of peritumoral lymphatic and blood vessel invasion in node-negative carcinoma of the breast. *J Clin Oncol.* 1990;8:1457-1465.
18. Clemente CG, Boracchi P, Andreola S, et al. Peritumoral lymphatic invasion in patients with node-negative mammary duct carcinoma. *Cancer.* 1992;15;69:1396-1403.
19. Pinder SE, Ellis IO, Galea M, et al. Pathological prognostic factors in breast cancer. III. Vascular invasion: relationship with recurrence and survival in a large study with long-term follow-up. *Histopathology.* 1994;24:41-47.
20. Lauria R, Perrone F, Carlomagno C, et al. The prognostic value of lymphatic and blood vessel invasion in operable breast cancer. *Cancer.* 1995;76:1772-1778.
21. Leitner SP, Swern AS, Weinberger D, et al. Predictors of recurrence for patients with small (one centimeter or less) localized breast cancer (T1a,bN0M0). *Cancer.* 1995;76:2266-2274.
22. De Mascarel I, Bonichon F, Durand M, et al. Obvious peritumoral emboli: an elusive prognostic factor reappraised: multivariate analysis of 1320 node negative breast cancers. *Eur J Cancer.* 1998;34:58-65.
23. Colpaert C, Vermeulen P, Jeuris W, et al. Early distant relapse in "node negative" breast cancer patients is not predicted by occult axillary lymph node metastases, but by the features of the primary tumour. *J Pathol.* 2001;193:442-449.
24. Colleoni M, Rotmensz N, Robertson C, et al. Very young women (<35 years) with operable breast cancer: features of disease at presentation. *Ann Oncol.* 2002;13:273-279.
25. Viale G, Zurrida S, Maiorano E, et al. Predicting the status of axillary sentinel lymph nodes in 4351 patients with invasive breast carcinoma treated in a single institution. *Cancer.* 2005;103:492-500.
26. Colleoni M, Rotmensz N, Maisonneuve P, et al. Prognostic role of the extent of peritumoral vascular invasion in operable breast cancer. *Ann Oncol.* 2007;18:1632-1640.
27. Cristofanilli M, Valero V, Buzdar AU, et al. Inflammatory breast cancer (IBC) and patterns of recurrence: understanding the biology of a unique disease. *Cancer.* 2007;110:1436-1444.
28. Rosen PP. *Rosen's Breast Pathology.* Philadelphia, PA: Lippincott-Raven; 1987.
29. Rosen PP. *Rosen's Breast Pathology.* 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.
30. Rosen PP. Tumor emboli in intramammary lymphatics in breast carcinoma: pathologic criteria for diagnosis and clinical significance. *Pathol Annu.* 1983;18:215-232.
31. Quiet CA, Ferguson DJ, Weichselbaum RR, et al. Natural history of node negative breast cancer: a study of 826 patients with long-term follow-up. *J Clin Oncol.* 1995;13:1144-1151.
32. Hanrahan EO, Valero V, Gonzales-Angulo AN, et al. Prognosis and management of patients with node-negative invasive breast carcinoma that is 1 cm or smaller in size (stage 1; T1a,bN0M0): a review of the literature. *J Clin Oncol.* 2006;24:2113-2122.
33. Viale G, Giobbie-Hurder A, Gusterson BA, et al. Adverse prognostic value of peritumoral vascular invasion: is it abrogated by adequate endocrine adjuvant therapy? results from two International Breast Cancer Study Group randomized trials of chemoendocrine adjuvant therapy for early breast cancer. *Ann Oncol.* 2010;21:245-254.
34. Eifel P, Axelson JA, Costa J, et al. National Institute of Health consensus development conference statement: adjuvant therapy for breast cancer, November 1-3, 2000. *J Natl Cancer Inst.* 2001;93:979-989.
35. National Comprehensive Cancer Network. Clinical practice guidelines in oncology, Version 1.2005, Breast Cancer. http// www.nccn.org/professionals/physician_gls/PDF/breast.pdf. Accessed May 30, 2013.
36. Goldhirsch A, Ingle JN, Gelber RD, et al. Thresholds for therapies: highlights of the St Gallen international expert consensus on the primary therapy of early breast cancer. *Ann Oncol.* 2009;20:1319-1329.
37. Haagensen C. *Disease of the Breast.* 2nd ed. Philadelphia, PA: Saunders; 1971.
38. Hoda SA, Hoda RS, Merlin S, et al. Issues relating to lymphovascular invasion in breast carcinoma. *Adv Anat Pathol.* 2006;13:308-315.
39. Lim CS, Alexander-Sefre F, Allam M, et al. Clinical value of immunohistochemically detected lymphovascular space invasion in early stage cervical carcinoma. *Ann Surg Oncol.* 2008;15:2581-2588.
40. Orbo A, Stalsberg H, Kunde D. Topographic criteria in the diagnosis of tumor emboli in intramammary lymphatics. *Cancer.* 1990;66:972-977.

DOI: 10.1309/AJCPOXKX67KRAOVM

41. Wolff AC, Hammond EH, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol.* 2013;31:3997-4013.
42. Rosner D, Lane WW. Should all patients with node-negative breast cancer receive adjuvant therapy? identifying additional subset of low-risk patients who are highly curable by surgery alone. *Cancer.* 1991;68:1482-1494.
43. Rosner D, Lane WW. Predicting recurrence in axillary-node negative breast cancer patients. *Breast Cancer Res Treat.* 1993;25:127-139.
44. Rosen PP, Groshen S, Saigo PE, et al. A long-term follow-up study of survival in stage I (T1N0M0) and stage II (T1N1M0) breast carcinoma. *J Clin Oncol.* 1989;7:355-366.
45. Rosen PP, Groshen S, Kinne WW, et al. Factors influencing prognosis in node-negative breast carcinoma: analysis of 767 T1N0M0/T2N0M0 patients with long-term follow-up. *J Clin Oncol.* 1993;11:2090-2100.
46. Joensuu H, Isola J, Lundin M, et al. Amplification of erbB2 and erbB2 expression are superior to estrogen receptor status as risk factors for distant recurrence in pT1N0M0 breast cancer: a nationwide population-base study. *Clin Cancer Res.* 2003;9:923-930.
47. Rivadeneira DE, Simmons RM, Christos PJ, et al. Predictive factors associated with axillary lymph node metastases in T1a and T1b breast carcinomas: analysis in more than 900 patients. *J Am Coll Surg.* 2000;191:1-8.
48. Van der Auwera I, Cao Y, Tille JC, et al. First international consensus on the methodology of lymphangiogenesis quantification in solid human tumours. *Br J Cancer.* 2006;95:1611-1625.
49. Anderson WF, Chu KC, Chang S, et al. Comparison of age-specific incidence rate patterns for different histopathologic types of breast carcinoma. *Cancer Epidemiol Biomarkers Prev.* 2004;13:1128-1235.
50. Anderson WF, Pfeiffer RM, Dores GM, et al. Comparison of age distribution patterns for different histopathologic types of breast carcinoma. *Cancer Epidemiol Biomarkers Prev.* 2006;15:1899-1905.

DOI: 10.1309/AJCPOXKX67KRAOVM