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Breast Carcinoma With Micropapillary Features: Clinicopathologic Study and Long-Term Follow-Up of 100 Cases

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To study the clinicopathologic characteristics and prognosis of invasive micropapillary carcinoma of breast (IMPC), 100 cases of invasive breast carcinoma with an IMPC component were reviewed. Compared with invasive ductal carcinoma, not otherwise specified, with similar histologic grades, carcinomas with IMPC were larger sized, had a higher lymph node metastasis rate with more nodes involved per case, and exhibited increased lymphovascular invasion. The presence of IMPC strongly correlated with the more aggressive behavior. No significant association was established between the proportion of the IMPC component and overall tumor size, histologic grade, lymph node metastasis rate, and distant metastasis, but a trend was noted. Long-term follow-up demonstrated a poorer 5-year and 10-year survival rate for patients with breast carcinoma containing an IMPC component. Breast carcinomas with micropapillary features are more aggressive tumors with a poorer prognosis. This specific structure should be carefully evaluated in the surgical pathology examination of breast carcinoma specimens.

Keywords: breast neoplasm; invasive micropapillary carcinoma; clinicopathologic characteristic; prognosis

The term invasive micropapillary carcinoma (IMPC) of the breast was first used in 1993 by Siriaunkgul and Tavassoli,[1] who described 9 examples of this lesion. Invasive micropapillary carcinoma is characterized by small papillary structures that lack true central fibrovascular cores and lie within empty stromal spaces. It is known for its high incidence of axillary lymph node metastasis, recurrence, and distant metastasis,[2,3] and is listed as an independent subtype of invasive breast carcinoma in the 2003 World Health Organization (WHO) histologic classification of tumors of the breast.

Although quite rare in its pure form, focal micropapillary growth has been reported in 3% to 6% of the more common types of invasive breast carcinomas.[4] No consensus has yet been reached on the IMPC volume required for its diagnosis, and there is a shortage of information about the behavior of tumors with a minor component of IMPC. We undertook a retrospective study of 100 cases of breast carcinoma with varying amounts of IMPC to explore their clinicopathologic characteristics and determine whether an increasing proportion of IMPC in breast carcinoma correlates with a more aggressive clinical behavior and worse prognosis.

Materials and Methods

Cases and Histopathology

We retrieved 100 cases of breast carcinoma with an IMPC component, diagnosed between 1989 and

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2001, from the archive of the Department of Breast Cancer Pathology and Research Laboratory, Cancer Hospital of Tianjin Medical University, Tianjin, China. In all cases, each tumor had been cut into multiple blocks with all tumor tissue embedded. Slides stained with hematoxylin and eosin (H&E) from all blocks for each tumor were reviewed by 3 senior breast pathologists (LF, YF, and R-GL) to verify the presence of IMPC according to the morphologic criteria described in the WHO histologic classification of breast tumors.[4] The specimens were allocated to 4 groups according to the amount of IMPC present in each tumor: tumors with less than 25%, tumors with 25% to 49%, tumors with 50% to 75%, and tumors with more than 75%. The type of non-micropapillary carcinoma making up the rest of each tumor was also recorded.

The IMPC component for each tumor was graded according to the Elston and Ellis[5] grading system as follows:

- grade I, no significant nuclear atypia and mitotic count of 1 or less per 10 high-power fields (HPF);
- grade II, moderate nuclear atypia and mitotic count of 2 to 3 per 10 HPF; and
- grade III, marked nuclear atypia and mitotic count of more than 4 or more per 10 HPF.

Lymphovascular invasion (LVI) was assessed during the review of the H&E sections and recorded as follows: negative, no IMPC cells in lymph vessels; positive, lymphatic vessel dilated by IMPC cells. The number of lymph nodes with metastasis, and the histologic type(s) of metastatic carcinoma were also recorded.

As a control group, 100 cases of invasive ductal carcinoma, not otherwise specified (NOS-IDC) that had been diagnosed during the same time period were randomly selected and studied in parallel.

Immunohistochemistry Analysis

All cases were examined immunohistochemically for receptors for estrogen and progesterone (both Zymed Laboratories, South San Francisco, California) by using the avidin-biotin-immunoperoxidase technique. Cases were scored positive if nuclear staining was present in 10% or more of the tumor cells.

Follow-Up and Statistics

Clinical information for all cases was retrieved from medical records and included family history of tumors, therapeutic regimens, recurrence, distant metastasis, and survival status.

Statistical analyses were performed for categoric variables by χ^2 and the Fisher exact test, when appropriate, and numeric variables by Student *t* test or 1-way analysis of variance. Kaplan-Meier univariate and Cox multivariate analyses were performed to calculate the survival rate.

Results

Clinical Information

The 100 cases of breast carcinoma with an IMPC component all occurred in women, and their mean age was 50 years (range, 30-72 years). Of these, 98 patients had breast masses, and 5 also had metastasis at the time of diagnosis to the supraclavicular lymph nodes in 3 patients, to the bone in 1, and to the liver in 1. The 100 patients with NOS-IDC of breast were all women, and their mean age was 51 years (range, 32-81 years).

Carcinoma With Micropapillary Features and Invasive Ductal Carcinoma, Not Otherwise Specified

A similar distribution of histologic grade was observed for carcinomas with micropapillary features and the control group of IDC-NOS, although there was some tendency toward higher grade for the IMPC group (Table 1). Tumors containing an IMPC component were of larger average size (3.38 vs 2.39 cm; $P < .001$), were more likely to exhibit lymph node metastasis (84.45% vs 50%; $P < .001$), and had spread to a greater number of lymph nodes in each case (14 vs 3; $P < .001$). Lymphvascular invasion was also much more apparent (69% vs 26%; $P < .001$) in tumors with an IMPC component (Table 1). The metastatic carcinomas had microscopic features similar to the primary tumors.

Proportion of Invasive Micropapillary Carcinoma and the Pathologic Features

The 100 cases of breast carcinoma with an IMPC component were allocated to 4 groups according to the amount of IMPC present (as described in Cases and Histopathology). Photomicrographs of representative tumors containing less than 25% IMPC

Table 1. Clinicopathologic Features of Carcinoma With Invasive Micropapillary Carcinoma Component and Invasive Ductal Carcinoma, Not Otherwise Specified

Factor	IMPC	NOS-IDC	χ^2	*P*
Mean tumor size (cm)	3.38	2.39		<.001[a]
Lymph nodes/case, No. positive	14	3		<.001[b]
Histologic grade, No. (%)				
I	31 (31)	30 (30)		
II	37 (37)	49 (49)		
III	32 (32)	21 (21)	3.974	.137
LN metastasis, No. (%)				
Positive	84 (84.8)	50 (50)		
Negative	15/99	50	27.469	<.001
LVI, No (%)				
Negative	31	74		
Positive	69 (69)	26 (26)	37.073	<.001
Estrogen receptor, No. (%)				
Positive	46 (46)	52 (52)		
Negative	54	48	0.720	.396
Progesterone receptor, No. (%)				
Positive	27 (27)	37 (37)	2.298	.130
Negative	73	63		
Mean follow-up, mon (range)	60.1 (4-199)	75.7 (7-170)		
Local recurrence, No. (%)	11/98 (11.2)	4 (4)	3.689	.055
Distant metastasis, No. (%)	38/98 (38.8)	28 (28)	2.586	.108
Died of disease, No. (%)	36/98 (36.7)	19 (19)	7.760	.005
Overall survival rate, %				
5 years	59	77		
10 years	48	52		

NOTE: IMPC = invasive micropapillary carcinoma component; LN = lymph node; LVI = lymphovascular invasion; NOS-IDC = invasive ductal carcinoma, not otherwise specified.
[a] $t = -3.570$; $P < .001$.
[b] $t = -7.038$; $P < .001$.

and more than 75% IMPC are illustrated in Figures 1A and 1B, respectively. The clinicopathologic features of tumors in each group are summarized in Table 2. Nearly one-half of tumors in this group consisted mostly or entirely of IMPC, and although not significantly different, these tumors had a tendency toward larger mean size, had a greater proportion of higher histologic grade, and had a greater proportion exhibiting lymph node metastasis, distant metastasis, and recurrence. These tumors also exhibited a much greater tendency for LVI ($P = .010$). The number of the lymph nodes with metastasis in each case ($P = .050$) and proportion of IMPC in the lymph nodes ($P = .010$) were positively associated with an increasing amount of IMPC component in the primary tumors (data not shown).

The type of carcinoma in association with the IMPC component included 68 cases of NOS-IDC, 2 of mucinous carcinomas, and 1 of invasive lobular carcinoma (Fig 2A). An IMPC component mixed with ordinary ductal carcinoma in situ (Fig 2B) was noted in 7, and the carcinomas in the remaining cases consisted entirely of IMPC.

Tumors With a Minor Component of Invasive Micropapillary Carcinoma

Our results indicated that a greater content of IMPC was associated with a trend toward more aggressive behavior. To determine if even a minor component of IMPC increased the aggressive behavior of a breast carcinoma, the clinicopathologic characteristics of the 14 cases containing less than 25% IMPC were compared with the 100 control cases of NOS-IDC (Table 3). Increased LVI ($P = .009$) and lymph node metastasis ($P = .018$) were identified in the IMPC cases, although no significant difference was found in the number of lymph nodes with metastasis per case and proportion of cases with distant metastasis. Five of the 14 cases

Table 2. Clinicopathologic Features of Carcinomas With Varying Amount of Invasive Micropapillary Carcinoma

		Amount of Invasive Micropapillary Carcinoma				
Factor	Total	<25%	25%-49%	50%-75%	>75%	*P*
Cases, No.	100	14	15	26	45	
Age, mean y	50	52	54	49	49	.340[a]
Tumor size, mean cm	3.384	2.65	2.46	3.177	4.04	.074[b]
Histologic grade						
I	100	8	5	9	9	
II		3	7	11	16	
II		3	3	6	20	.095[c]
LN metastasis, No	99					
Negative		2	4	5	4	
Positive		11	11	21	41	.434[d]
LVI, No.	100					
Negative		5	7	12	7	
Positive		9	8	14	38	.010[e]
Recurrence, No.	98					
Yes		0	1	2	8	
No		13	13	24	37	...[f]
Distant metastasis, No.	98					
Yes		3	5	7	23	
No		10	9	19	22	.120[g]

NOTE: LN = lymph node; LVI = lymphovascular invasion.
[a] $F = 1.132$; $P = .340$ (1-way analysis of variance)
[b] $F = 2.389$; $P = .074$ (1-way analysis of variance).
[c] The comparison between <49%, 50%-75%, and >75% groups: $\chi 2 = 7.512$; $P = .095$.
[d] The comparison between <49% and >50% groups: $\chi 2 = 0.613$; $P = .434$.
[e] The comparison between <49%, 50%-75% and >75% groups: $\chi 2 = 9.270$; $P = .010$.
[f] Not statistically significant.
[g] $\chi 2 = 5.828$; $P = .120$.

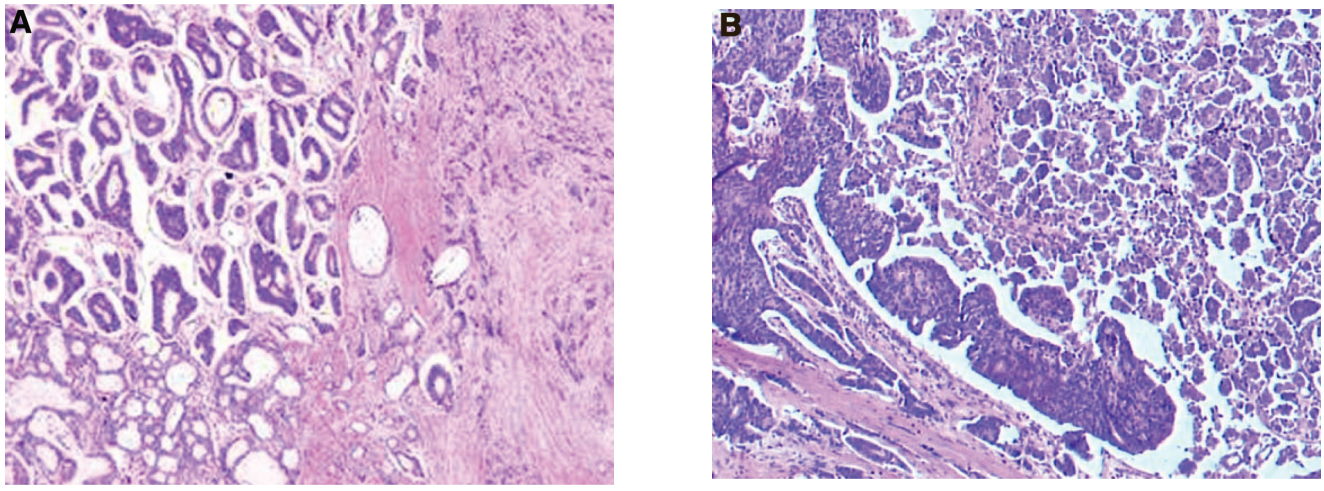

Figure 1. (A) Minor invasive micropapillary carcinoma component (IMPC) of less than 25% and invasive ductal carcinoma, not otherwise specified (NOS-IDC) in the right (hematoxylin and eosin, ×40 original magnification). (B) IMPC components exceeding 75% in the right and NOS-IDC components in the left (hematoxylin and eosin, ×40 original magnification).

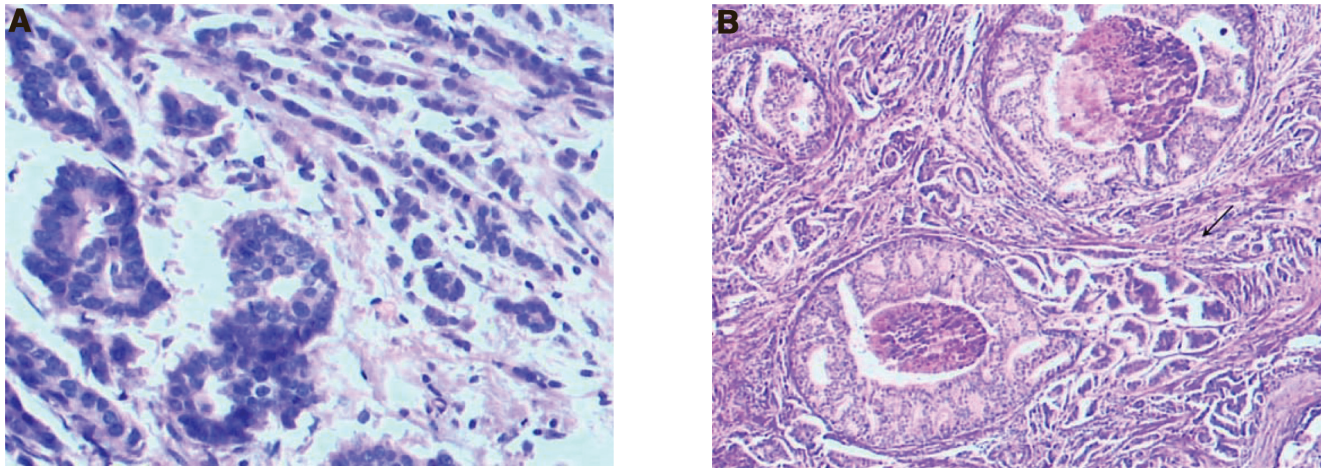

Figure 2. Invasive micropapillary carcinoma (IMPC) associated with non-micropapillary components. (A) The IMPC components are admixed with invasive lobular carcinoma (hematoxylin and eosin, ×200 original magnification. (B) Ductal carcinoma in situ (grade II) are surrounded by few IMPC components (arrow, hematoxylin and eosin, ×100 original magnification.

Table 3. Clinical and pathologic Features of Tumors with Minor Invasive Micropapillary Carcinoma Component and Invasive Ductal Carcinoma, Not Otherwise Specified

Factor	IMPC < 25%	NOS-IDC	χ^2	*P*
No.	14	100		
Positive LN/case, No LN metastasis	8/13	3		.149[a]
Positive	11	50		
Negative	2/13	50	5.549	.018
LVI				
Positive	5	74		
Negative	9	26	6.757	.009
Distant metastasis	3/13	28	0.002	.965
Died of disease	3/13	19	>0.001	>.99

NOTE: IMPC = invasive micropapillary carcinoma; LN = lymph node; LVI = lymphovascular invasion; NOS-IDC = invasive ductal carcinoma, not otherwise specified.
[a] $t = 1.536$; $P = .149$.

contained only 5% to 10% IMPC; however, each exhibited extensive LVI (Fig 3A), and 1 also presented with tumor tissue in blood vessels (Fig 3B).

Treatment and Follow-Up of Patients With an Invasive Micropapillary Carcinoma Component

Radical mastectomy was performed in 52 patients, modified radical mastectomy in 47, and simple mastectomy in 1. Forty patients completed the full course of neoadjuvant and adjuvant chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil; paclitaxel; cyclophosphamide, Adriamycin [Pharmacia S.p.A, Milan, Italy], and 5-fluorouracil; or cyclophosphamide, vinblastine, and 5-fluorouracil), 49 patients had only adjuvant chemotherapy, and 72 patients were offered radiation therapy. Tamoxifen endocrine therapy was given to 52 patients: 30 tumors were positive for estrogen receptor and 17 tumors were positive for progesterone receptor.

Follow-up information was available for 98 patients, with a mean follow-up time of 60.1 months (range, 4-199 months; Table 1). Of these, 11 patients (11.2%) showed local recurrence within a mean time of 26.4 months (range, 4-85 months), and 38 patients (38.3%) had distant metastasis within 90 months (mean, 36 months). Thirty-six patients (36.7%) died of breast cancer, and 2 died of heart disease. The survival of 59% at 5 years and 48% at 10 years (Table 1) was lower than the survival rates for the control group ($P = .004$; Fig 4A).

Kaplan-Meier univariate survival curve analysis showed that LVI was adversely associated with patient survival ($P = .026$; Fig 4B). Patients who completed their chemotherapy and tamoxifen therapy lived longer ($P = .045$, Fig 4C; $P = .037$, Fig 4D); however, combined neoadjuvant and adjuvant chemotherapy did not demonstrate additional benefit to the patients compared with those who received adjuvant chemotherapy alone ($P > .05$, data not

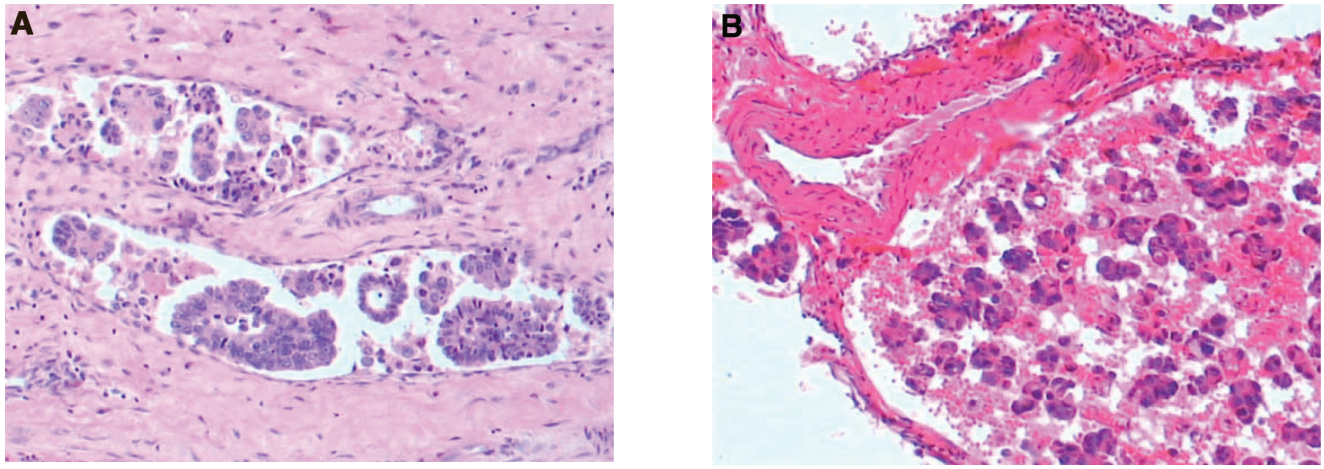

Figure 3. Lymphovascular invasion and blood vessel invasion. (A) Lymphovascular invasion: 2 lymphatic vessels were dilated by micropapillary components with a vein in middle (hematoxylin and eosin, ×100 original magnification). (B) Vascular invasion: invasive micropapillary carcinoma clusters in a small vein, and an arteriole in the left (hematoxylin and eosin, ×100 original magnification).

shown). Tumor size, proportion of IMPC, histologic grade, and lymph node metastasis did not significantly correlate with survival ($P > .05$, data not shown). The Cox model of multivariate survival analysis also indicated that the risk of death was increased with increased LVI, whereas tamoxifen therapy improved survival (data not shown).

Discussion

Since IMPC of the breast was first described in 1993 by Siriaunkgul and Tavassoli, studies have explored the nature of this rare subtype of breast carcinoma. It is generally believed that IMPC is an aggressive tumor with poor clinical outcome, but its biologic behavior has not been elucidated well. Because IMPC is more commonly found as a component of other types of breast carcinoma, it would be of practical importance to determine the extent to which the presence of this subtype governs the clinical behavior of such tumors, particularly for those carcinomas with only a minor component of IMPC.

To ensure a more accurate estimate of the percentage of the IMPC component in the tumors, we selected 100 cases in which all of the tumor tissue had been embedded. Given that no criteria have been established in terms of the proportion of IMPC within a tumor that is required to make the diagnosis of IMPC, we have described these 100 cases as "invasive breast carcinoma with micropapillary features." Compared with the 100 cases of NOS-IDC, which were studied in parallel, carcinomas with micropapillary features presented as larger tumors, had a higher lymph node metastasis rate with more nodes involved per case, and exhibited increased LVI. Follow-up (mean, 60.1 months) demonstrated a poorer 5-year and 10-year survival compared with NOS-IDC, with more patients dying of disease (Table 1). These findings are consistent with those of Paterakos et al[6] and Zekioglu et al,[7] indicating a subtype of more aggressive tumors.

The 2003 WHO histologic classification of breast tumors does not specify the amount of IMPC required for a diagnosis of IMPC,[4] and no consensus opinion has been reached in the literature. Middleton et al[8] and Zekioglu et al[7] proposed that the IMPC component be more than 75% of the total tumor volume before IMPC is diagnosed. De La Cruz et al[9] stated that the diagnosis of IMPC should be made when more than 33% of tumor volume is IMPC. Nassar et al[10] failed to identify significant differences in node status, estrogen receptor status, tumor size, histologic grade, or LVI between 2 groups of tumors with more or less than 50% IMPC.

Our study found no statistically significant differences among the 4 groups of breast carcinoma with different proportions of IMPC in terms of tumor size, histologic grade, or rates of nodal metastasis, recurrence, or distant metastasis (Table 2), although there was a notable trend in which an increasing amount of IMPC was associated with an increase in each of those indicators. The amount of

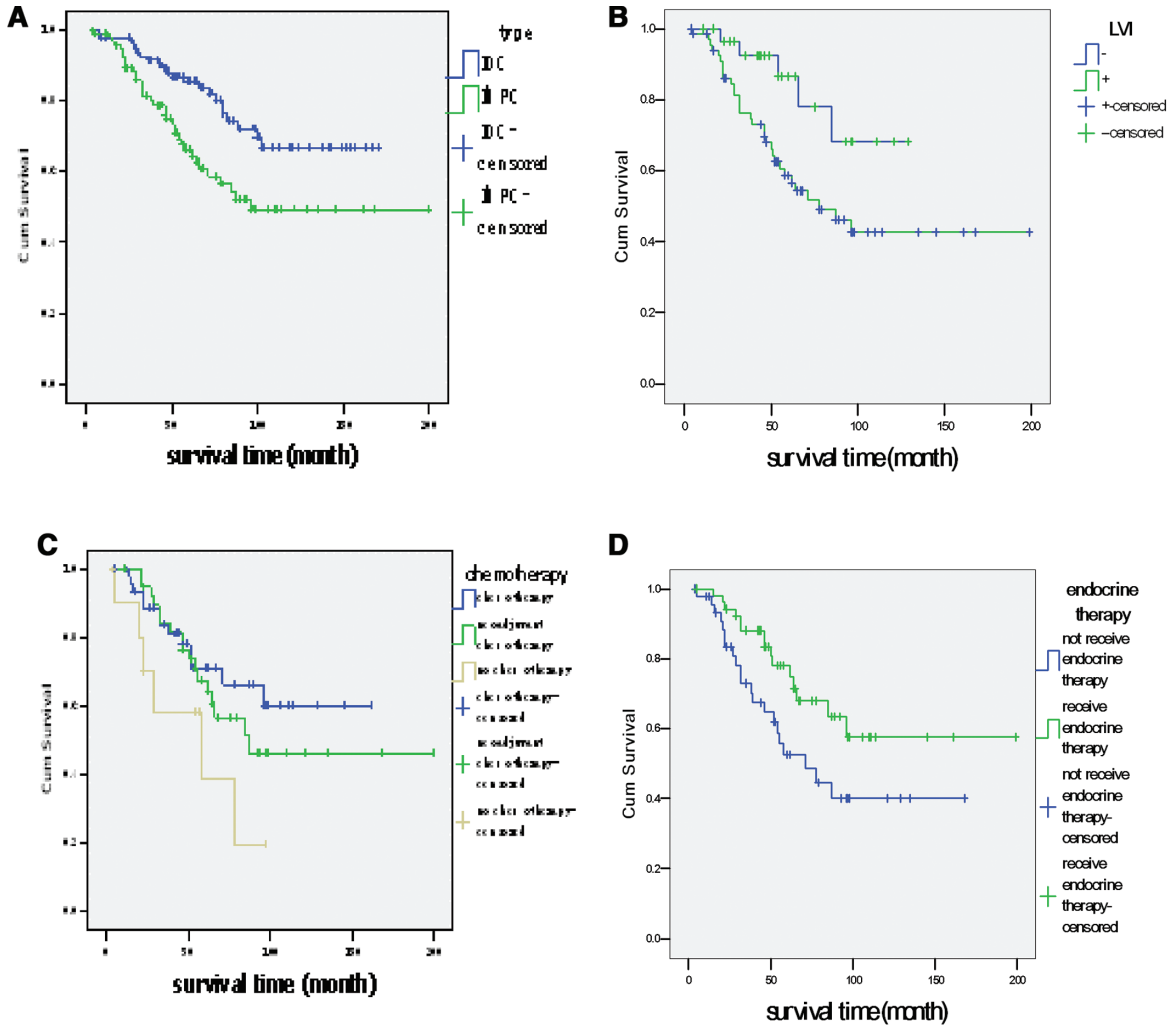

Figure 4. (A) Cumulative survival rate curve of invasive micropapillary carcinoma (IMPC) and invasive ductal carcinoma (IDC; $P = .004$). (B) Lymphovascular invasion (LVI) and survival ($P = .026$). (C) Chemotherapy and survival ($P = .045$). (D) Tamoxifen endocrine therapy and survival ($P = .037$).

IMPC did correlate strongly with the number of the lymph nodes with metastasis per case ($P = .005$) and the proportion of IMPC components in the positive lymph nodes ($P = .010$). These results suggest that the amount of IMPC present plays at least some role in the clinical behavior of these tumors. Further studies involving additional cases of invasive breast carcinoma with micropapillary features should help to resolve this question. Lymphovascular invasion varied among the 4 groups, probably due to the small number of cases in each group, and additional studies are also required to validate this variable.

Although it appears that breast carcinomas with increasing amounts of IMPC trend toward more aggressive behavior, we also wanted to examine the impact IMPC has on tumor behavior by comparing the 14 cases of breast carcinoma that had less than 25% IMPC with the 100 cases of non-micropapillary NOS-IDC. The proportion of tumors with the same histologic grade in these 2 groups of carcinomas was about the same. We observed that LVI and the lymph node metastasis rate of the IMPC tumors were significantly higher than the NOS-IDC cases (Table 3). Indeed, 5 cases with only 5% to 10% IMPC exhibited extensive LVI in histologic sections and 1 case also presented with vascular invasion.

Continuing accumulation of data is required to further understand the biologic differences between

tumors with a minor IMPC component and NOS-IDC, but the evidence strongly suggests that the presence of IMPC itself is strongly associated with the aggressive behavior of the tumor. We propose that any breast carcinoma with IMPC differentiation should be properly reported, and until further studies become available, the percentage of the IMPC component should be specified in a routine surgical pathology report.

The rates of recurrence, distant metastasis, and mortality associated with IMPC have been reported with great variation.[7,9-12] Our findings of recurrence (11.2%), distant metastasis (38.8%), and cancer death (36.7%) are more consistent with those studies that have used large sample sizes and long periods of follow-up.[10,12]

Rosen[13] believed LVI indicated a poor prognosis for breast cancer patients. The univariate and multivariate survival analyses of this study showed that LVI was adversely associated with the survival of IMPC patients ($P < .01$), supporting that assertion. Guo et al[14] found that IMPC tumor cells are capable of synthesizing vascular endothelial growth factor-C, which induces the growth of new lymphatic capillaries. The newly formed lymphatic vessels are purported to be more vulnerable to tumor invasion and facilitate metastasis to regional lymph nodes. Our data did not prove lymph node metastasis to be an independent prognostic factor, and this was probably due to a sample bias of this particular patient pool. Additional studies are necessary to elucidate this important issue.

Pettinato et al[12] suggested preoperative neoadjuvant chemotherapy would improve survival. In our study, univariate survival analysis showed that neoadjuvant chemotherapy did not demonstrate an additional survival benefit in the 40 patients who received both preoperative and postoperative chemotherapy compared with the 49 patients who only completed postoperative adjuvant chemotherapy. Standard cyclophosphamide, methotrexate, and 5-fluorouracil neoadjuvant chemotherapy was given to 36 of the 40 patients, which raised a question about whether the classic neoadjuvant chemotherapy is suitable for IMPC patients. Finding effective new chemotherapy regimens is one of our objectives in future research. Univariate and multivariate analysis showed that patients had greater survival when given tamoxifen endocrine therapy, suggesting that tamoxifen endocrine therapy be offered to IMPC patients with positive estrogen or progesterone receptors, or both.

Conclusion

Carcinoma with micropapillary features is an aggressive subtype of breast carcinoma with a poor prognosis. The presence of IMPC, even when it is only a minor component, is associated with the aggressive behavior of the tumor, a fact that should be properly evaluated in a routine surgical pathology examination. Additional studies including controlled tumor staging and treatment regimens and with longer follow-up are required to further explore the clinicopathologic differences between the tumors with minor IMPC components and NOS-IDC. Studies are also needed to further assess the association between the amount of IMPC and the prognosis of this uncommon type of breast carcinoma.

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