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The presence of retraction clefts correlates with lymphovascular invasion and lymph node metastasis and predicts poor outcome: analysis of 2497 breast cancer patients

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Abstract

Some invasive breast carcinomas are surrounded by a clear space that separate the tumor cells from the adjacent stroma, similar to invasive micropapillary carcinoma (IMPC), but lack the thin strands of connective tissue that separate the cells and characteristic "inside-out" growth pattern of IMPC on immunohistochemical stain for EMA. We consider the presence of the retraction clefts a common phenomenon that may present as a precursor stage of IMPC (PSIMPC). In this

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study, a total of 2497 cases of invasive breast carcinomas were prospectively collected. Among 2497 cases of breast cancer, 949 (38.0%) cases were PSIMPC, 200 (8.0%) cases were IMPC and 1348 (54.0%) cases were IBC-NST. LVI was seen in128 of 200 (64%) IMPC and 364 of 948 (38.0%) PSIMPC, in contrast to 246 of 1341 (18%) IBC-NST (P<0.001). Lymph node metastasis was seen in 147 of 200 (73.4%) IMPC and 551 of 949 (58%) PSIMPC, in contrast to 563 of 1345 (42%) IBC-NST (P<0.001). The 5-year disease-free survival (DFS) and overall survival (OS) of PSIMPC were 76.8% and 87.6%, compared to 63.2% and 85.9% in IMPC, 86.2% and 93.7% in IBC-NST. PSIMPC demonstrated a more favorable DFS and OS compared to IMPC, but worse DFS and OS compared to IBC-NST. Cox and logistic regression analysis showed that PSIMPC was an independent predictor of DFS and OS. Our findings suggest that the presence of retraction clefts is a precursor state of IMPC, exhibiting IMPC-like features, such as higher incidence of lymphovascular invasion, lymph node metastasis and more aggressive clinical behavior.

Keywords

breast cancer; retraction clefts; invasive micropapillary carcinoma; lymphovascular invasion; lymph node metastasis

1. Introduction

Invasive micropapillary carcinoma (IMPC) is a rare special histologic subtype of breast cancer, accounting for approximately 3% to 8% of all breast cancers [1, 2]. It consists of small, hollow, or morule-like clusters of cancer cells surrounded by clear stromal space [3]. The cells exhibit reversed polarity with the glandular epithelial cells located on the outer surface of the cell nests, revealed by immunohistochemical stain for epithelial membrane antigen (EMA). IMPC is associated with higher incidence of lymphovascular invasion (LVI), lymph node metastasis and poor prognosis [4, 5].

Some invasive breast cancers have tumor cell clusters surrounded by clear stromal space similar to IMPC, but lack the morphological and immunohistochemical characteristics of IMPC. On formalin-fixed paraffin-embedded tissue sections, there are often clear spaces separating tumor cell clusters from adjacent stroma, which can be difficult to distinguish from LVI [6, 7]. Previous studies have shown that the presence of these so-called retraction clefts (RC), may be important for the histologic diagnosis and overall survival of prostate cancer and oral squamous carcinoma [8, 9,10], in general, RCs are considered artifactual, which may be due to inadequate tissue fixation and tissue contraction. However, characteristic retraction clefts around the tumor cell nests may be found even on frozen section of invasive breast carcinoma [6], and this phenomenon may have special significance, rather than artificial products [11].

In this prospective study, we assessed whether the presence of retraction clefts in tumors without the characteristic histological features of IMPC, is associated with lymphovascular invasion, lymph node metastasis and outcomes in a large consecutive series of invasive breast cancers.

2. Materials and methods

2.1 Clinical Data

A total of 2497 cases of invasive breast carcinomas were prospectively collected from Tianjin Medical University Cancer Institute& Hospital (TMUCIH). Patients were diagnosed and had surgical treatment between January 2005 and December 2006. Hematoxylin and eosin (H&E) stained slides were reviewed by three breast pathologists (HQ Jia, WD Li, and L Fu) to assess the diagnosis according to the WHO Classification of Tumors of the Breast [12], including histologic type, grade, LVI and LN involvement.

Special histologic subtypes of invasive breast cancer other than IMPC were excluded. IMPC showed reversed polarity, and the glandular epithelium was located on the outer surface of tumor cell nests labeled by immunohistochemical stain for EMA (Figure 1A&1B). Cases with clear spaces around tumor cell clusters but lack characteristic features of IMPC were identified as PSIMPC. As long as there is any proportion of RC in the tumor, it is classified as IMPC or PSIMPC according to the morphological features of the tumor cells and their arrangements, cases that difficult to distinguish were further identified as IMPC or PSIMPC by immunohistochemistry with EMA. Cases with both IMPC and PSIMPC components were classified as IMPC. In order to compare the characteristics of IMPC and PSIMPC, a case with both IMPC and PSIMPC components is illustrate in Figure 1 (Figure 1C&1D). In selected cases, if LVI and RC were difficult to distinguish according to the morphological features, immunohistochemical stain for D2-40 was performed to support the presence and absence of LVI [13, 14]. Retraction clefts result in clear spaces is seen around DCIS, and D2-40 immunohistochemistry can highlight the myoepithelial cells around breast DCIS. In very difficult cases, additional markers for myoepithelial cells and lymphatic vessels (such as p63, SMMHC and CD31) were performed to avoid misinterpretation of LVI.

2.2 Immunohistochemistry

The 4 μm sections of formalin fixed and paraffin embedded sections were analyzed by immunohistochemistry. Immunocytochemical stain for EMA (clone E29, Dako, Denmark) was performed on PSIMPC and IMPC which were difficult to distinguish according to the morphological features.

D2-40 (clone D2-40, Zymed) immunohistochemical stain highlights endothelial cells, which was performed to confirm the presence of LVI when necessary (Figure 1E&1F). Estrogen receptor (ER) antibody (clone SP1) and progesterone receptor (PR) antibody (clone SP2) were from Zymed. Immunohistochemical analysis of human epidermal growth factor receptor 2 (HER-2) used DAKO HercepTest TM (Denmark). Assessment of ER, PR and HER2 followed the American Society of Clinical Oncology /College of American Pathologists guidelines [15, 16].

2.3 Statistically analyze

Mann-Whitney U test and Kruskal-Wallis test were used to compare the clinicopathological characteristics between the two groups of variables and the multiple groups of variables. Cox proportional risk model was used to evaluate the effect of tumor variables on survival

rate. Univariate and multivariate logistic regression models were applied to analyze the predictors for disease-free survival and overall survival. Kaplan-Meier method calculated the DFS and OS curves, and the differences between the curves were evaluated using a log-rank test. 2-sided $P<0.05$ was identified statistical significance. SPSS 22.0 software for Windows (IBM, NY, USA) was used for statistical analysis.

3 Results

3.1 Clinicopathologic characteristics

Table 1 shows the clinicopathologic characteristics of PSIMPC and IMPC. Among a total of 2497 cases, 949 (38%) and 200 (8%) showed features of typical PSIMPC and IMPC, respectively. The range of PSIMPC component was 1%-95% of the tumor, with a median proportion of 15% (mean ±standard error of mean, 23.6 ± 0.8). The IMPC component was 1% −100% of the tumor, with a median proportion of 50% (mean ±standard error of mean, 53.7 ± 2.2). In most (68%) PSIMPC cases, the proportion of PSIMPC was less than 25%. In only 14% of PSIMPC cases, PSIMPC constituted more than 50% of the tumor, in contrast to nearly half (49%) of cases of IMPC, the IMPC component constituted more than 50% of the tumor ($P<0.001$).

Patient's age was not significantly different between PSIMPC and IMPC, IBC-NST group. Compared to IBC-NST, PSIMPC had significantly larger tumor size ($P<0.001$) and higher histological grade ($P<0.001$). PSIMPC had significantly higher incidence of LVI ($P<0.001$) and LN($P<0.001$) metastasis comparing to IBC-NST. LVI was seen in 364 (38.0%) of 949 PSIMPC and 128 (64%) of 200 IMPC, in contrast to 246 (18%) of 1341 IBC-NST. LN metastasis was seen in 551 (58%) of 949 PSIMPC and 147 (73.4%) of 200 IMPC, in contrast to 563 (42%) of 1345 IBC-NST ($P<0.0001$). The rates of LVI and LN metastasis in PSIMPC were significantly higher than those in IBC-NST, but lower than those in IMPC.

IMPC was more frequently ER and PR positive than PSIMPC and ($P=0.002$ for ER and $P=0.028$ for PR). There was no significant difference in ER expression between PSIMPC and IBC-NST($P=0.053$). While the expression of PR in IBC-NST is higher than that of PSIMPC($P=0.003$). The presence of PSIMPC showing significant positive correlation with HER-2 status based on immunohistochemistry, compared to IBC-NST($P<0.001$). The rates of locoregional recurrence, distant metastasis and breast cancer related death in PSIMPC were significantly higher than those in IBC-NST ($P<0.001$).

3.2 Correlation of PSIMPC distribution in tumor with clinicopathologic characteristics

PSIMPC cases were further divided into three groups based on the distribution of PSIMPC in the tumor: both peripheral and internal group, peripheral only group and internal only group. Examples of the different distributions of PSIMPC are illustrated in Figure 2. The proportion of PCIMPC in the both peripheral and internal group was significantly higher than that in the peripheral only and internal only groups ($P<0.001$).

Comparison of clinicopathological characteristics of the three groups is summarized in Table 2. Internal only group was associated with less frequent LVI ($P<0.001$) and LN metastasis ($P<0.001$) than the other two groups. Both peripheral and internal group was less frequently

positive for ER and PR (P=0.005 and P=0.006), and decreased expression of HER-2 status based on immunohistochemistry (P=0.024). No significant correlation in patient age, tumor size, histologic grade and regional recurrence/ distant metastasis and death of disease was observed among the three groups.

3.3 Correlation of proportion in PSIMPC with clinicopathologic characteristics

According to the proportion of PSIMPC in tumors, we divide it into four categories: ≤25%,26-50%, 51-75%, 76-100% (Table 3). We found no significant correlation between the proportion of PSIMPC and age, tumor size, histological grade, LVI and LN involvement. High PSIMPC proportion was significantly associated with negative ER and PR expression (P<0.001). The proportion of PSIMPC showed a statistically highly significant correlation with HER-2 status based on immunohistochemistry, HER-2 expression is higher in tumors with high PSIMPC proportion than in tumors with low PSIMPC proportion (P<0.001).

The rates of regional recurrence, distant metastasis and death of disease were not significantly associated with proportion of PSIMPC (P=0.731 and P=0.143).

3.4 Survival Analysis

The median follow-up was 50 months (range1-180 months) in PSIMPC, 48 months (range 1-157 months) in patients with IMPC and 53 months (range 1-160 months) in IBC-NST. The 5-year DFS and OS for patients with PSIMPC were 76.8% and 87.6%, compared to 63.2% and 85.9% in IMPC (P=0.001 for DFS and P=0.008 for OS), 86.2% and 93.7% in IBC-NST (P<0.001 for DFS and P<0.001 for OS). Patients with PSIMPC demonstrated a more favorable DFS and OS compared to IMPC, but worse DFS and OS compared to IBC-NST (Figure 3A&3B).

On Cox regression multivariate analyses, tumor size (P=0.001), LN metastasis (P<0.001), LVI (P=0.001) and PSIMPC (P=0.029) were independent factors for disease-free survival (Table 4). For overall survival, tumor size (P=0.003), histological grade (P=0.001), LN metastasis (P<0.001), the presence of LVI (P<0.001), and the presence of PSIMPC (P=0.016) were independent factors (Table 4).

Among patients with PSIMPC, using Cox regression multivariate analyses, we found that tumor size (P<0.001 and P<0.001 respectively), LVI (P<0.001 and P=0.004 respectively), LN metastasis (P=0.006 and P<0.01 respectively) were significantly associated with disease-free survival and overall survival (Table 5).

Kaplan Meier was used to estimate disease-free survival and overall survival. No significant difference in disease-free survival and overall survival was found among different proportions of PSIMPC (P=0.645 and P=0.154) (Figure 3C&3D) and different distribution of PSIMPC (P=0.279 and P=0.179).

4. Discussion

In this study, we found that the presence of retraction clefts in invasive breast carcinoma, without characteristic IMPC features, even as a small proportion, was significantly

associated with lymphovascular invasion and lymph node metastasis, features similar to that of IMPC. Importantly, we found a significant association between the distribution of retraction clefts and LVI and LN metastasis. Retraction clefts located in both peripheral and internal area of the tumor demonstrated more aggressive behavior as measured by LN metastasis and LVI, compared to peripheral only and internal only groups. The proportion of the retraction clefts, however, was not significantly associated with LVI, LN metastasis, disease free survival and overall survival.

The mechanism of retraction clefts is not fully understood. Some studies suggest that this phenomenon is artifactual due to formalin fixation and tissue processing. However, retraction clefts in invasive breast carcinoma also exist on frozen sections [6], indicating that they are real spaces, not just caused by formalin fixation.

The presence of a wide range of retraction clefts in prostate cancer was correlated with tumor characteristics that suggest the tumor is more aggressive and a shorter recurrence free survival [17]. The micropapillary morphology in invasive urothelial carcinoma can predict the presence of infiltration. Even if there is no typical micropapillary morphology, significant retraction in invasive urothelial carcinoma may be associated with more aggressive disease [18].

The presence of retraction clefts in breast cancer may be a morphological reflection of changes in tumor-stromal interactions leading to tumor progression and lymphatic spread. Previous studies have shown that the presence of retraction clefts is associated with LVI and predicts lymph node metastasis and poor prognosis in early stage breast cancer [19]. Essentially all inflammatory breast cancer patients present with lymph node involvement and one-third of patients already have distant metastasis at initial diagnosis [20]. The author found that a tumor extrinsic factor, notably tumor-associated macrophages, promotes and contributes to inflammatory breast cancer’s extreme metastatic phenotype. Retraction clefts and tumor-stromal interactions may lead to lymphatic spread in breast cancer, but the mechanism need further elucidated.

In the current study, we found that the presence of retraction clefts in breast cancer was associated with the presence of LVI and LN metastasis, consistent with previous studies [21]. In addition, we found that the presence of retraction clefts was negatively associated with ER and PR expression.

We propose that invasive breast carcinoma with retraction clefts may represent the precursor state of IMPC (PSIMPC). In addition, retraction clefts correlated with lymphovascular invasion. For tumor with the retraction clefts, it is possible to may benefit from angiogenesis inhibitors. PSIMPC was an independent predictor in this cohort, significantly associated with worse disease-free survival and overall survival than IBC-NST, but better outcomes comparing to IMPC.

In conclusion, we revealed that the presence of retraction clefts in breast carcinomas was significantly correlated with LVI, LN metastases, and poor outcome. Retraction clefts may be part of the early stage of lymphovascular invasion of breast cancer cells. We recommend

the presence of retraction clefts should be mentioned in the pathology report to guide precise treatment.

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Highlights

- Some invasive breast carcinomas are similar to invasive micropapillary carcinoma (IMPC).
- We consider the presence of the retraction clefts a common phenomenon that may present as a precursor stage of IMPC (PSIMPC).
- PSIMPC demonstrated a more favorable DFS and OS compared to IMPC, but worse DFS and OS compared to IBC-NST.
- Our findings suggest that the presence of retraction clefts is a precursor state of IMPC, exhibiting IMPC-like features and more aggressive clinical behavior.

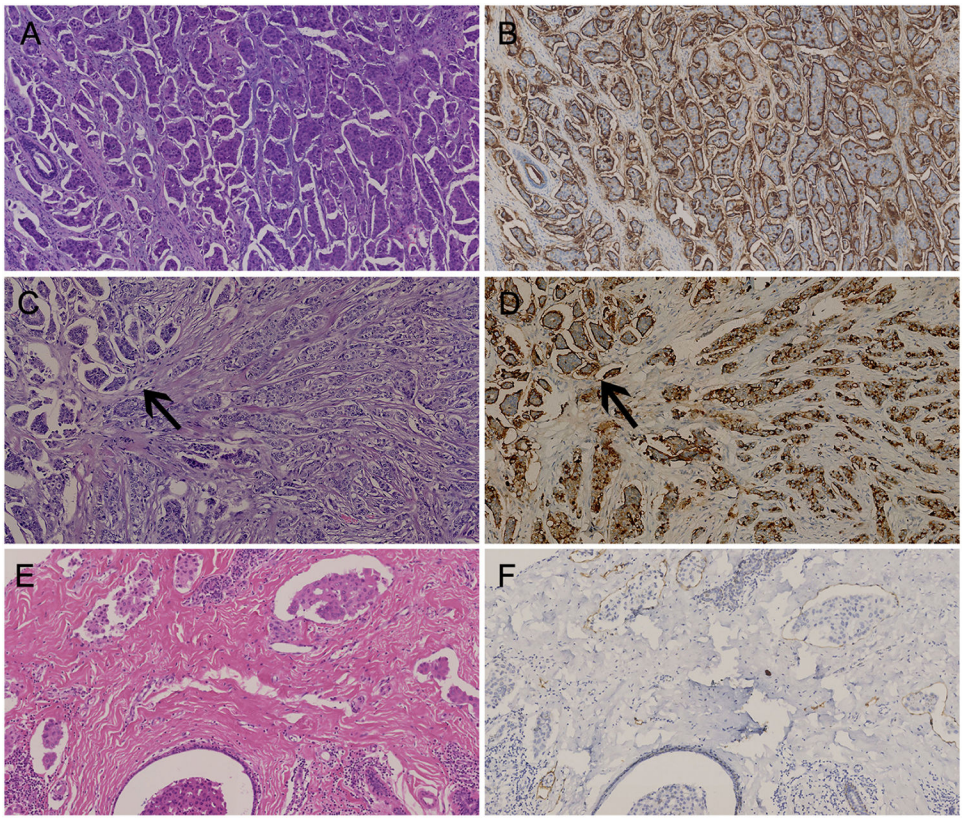

Figure 1.

Invasive micropapillary carcinoma (IMPC) showing the characteristic separated from the stroma by a clear space (A, H&E, ×100), and immunohistochemical stains for epithelial membrane antigen (B, immunohistochemical staining, ×100), mark the polarity reversal with the luminal aspect of the cell present on outer surface of the cluster. The upper left part (marked by arrow) is IMPC, and the rest is shown as invasive breast carcinoma with retraction cleft (C, H&E, ×100), EMA immunohistochemical staining showed that the upper left part (marked by arrow) was IMPC with reversed polarity, and the rest lack the characteristic of reversed polarity (D, immunohistochemical staining, ×100). Invasive breast carcinoma with lymphatic vessels (E, H&E, ×100), lymphatic endothelial cells immunohistochemical labeled by D2-40(F, immunohistochemical staining, ×100).

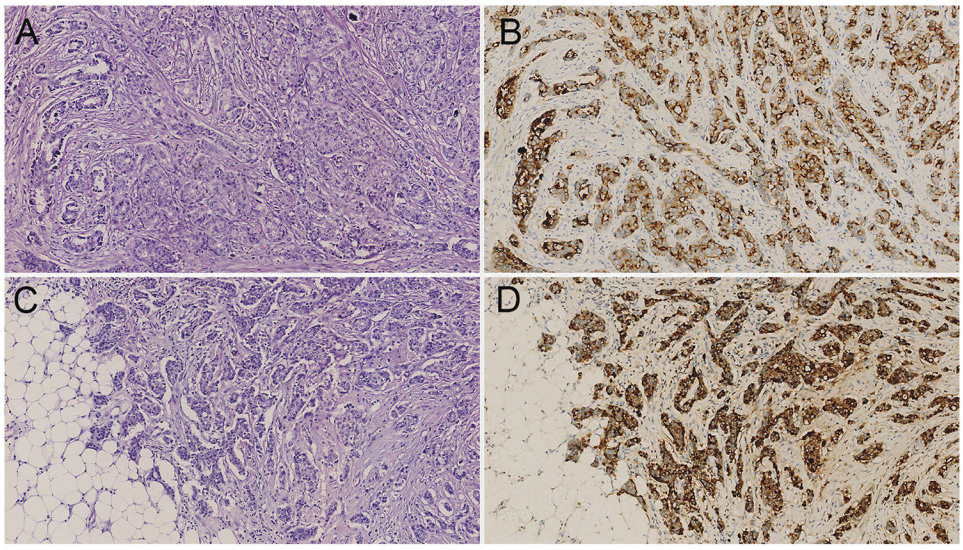

Figure 2.

PSIMPC located in the internal of tumor (A, H&E, ×100), RC located in the periphery of tumor and cancer cells infiltrate marginal adipose tissue (C, H&E,×100). Note the diffuse EMA immunoreactivity in the tumor cells, lack the polarity reversal architecture (B&D, immunohistochemical staining, ×100).

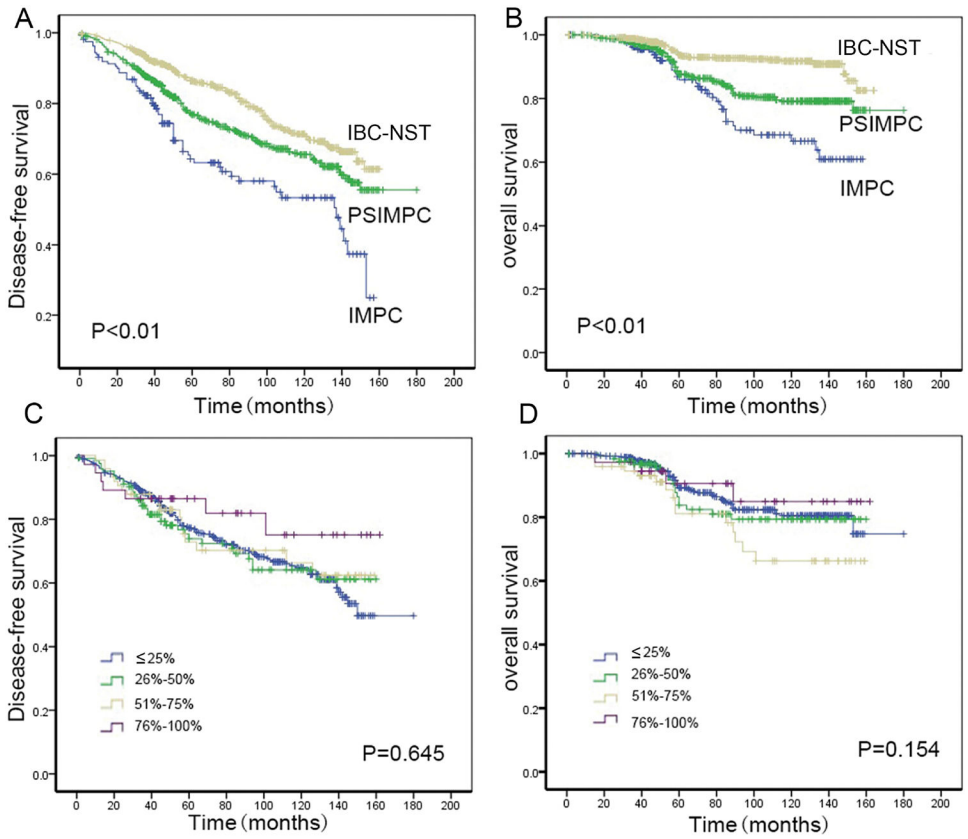

Figure 3.

Patients with PSIMPC demonstrated a more favorable DFS and OS compared to IMPC, but unfavorable disease-free survival and disease-free survival compared to IBC-NST without these features (P<0.01 and P<0.01). Kaplan-Meier estimates disease-free survival and overall survival, and compares four different proportions of PSIMPC. No significant difference was found in different proportions of PSIMPC (P=0.645 and P=0.154) (Figure 3C&3D).

Table 1.

Clinicopathologic characteristics of PSIMPC、 IMPC and IBC-NST

Characteristics	PSIMPC (n,%)	IMPC(n,%)	IBC-NST (n,%)	P^a/P^b
	949(38)	200 (8)	1348(54)	
Age at diagnosis				0.482/0.077
≤50	453(48)	90 (45)	694 (52)	
> 50	496(52)	111 (55)	654 (48)	
Tumor size (mm)				0.530/<0.001
≤20	310(33)	58 (30)	591(44)	
20-50	562(60)	124(64)	680 (51)	
> 50	65(7)	12(6)	60(5)	
PSIMPC / IMPC proportion				<0.001
⩽25%	648(68)	48 (24)	/	
26-50%	167(18)	55(27)	/	
51-75%	91(10)	38(19)	/	
76-100%	43(4)	59(30)	/	
LN				<0.001/<0.001
−	398(42)	53 (26)	782(58)	
+	551(58)	147 (74)	563 (42)	
LVI				<0.001/<0.001
−	584(62)	72(36)	1095 (82)	
+	364(38)	128(64)	246(18)	
TNM stage				<0.001/<0.001
1	173(19)	23(12)	400 (30)	
2	455(49)	68(34)	649 (48)	
3/4	308(33)	106(54)	290 (27)	
Histologic Grade				0.364/<0.001
I	56(6)	17 (11)	160(13)	
II	694(79)	109(73)	926(75)	
III	133(15)	24 (16)	144 (12)	
ER				0.002/0.053
−	239(26)	30(15)	319(25)	
+	685(74)	167(85)	977(75)	
PR				0.028/0.003
−	285(31)	45(23)	325(25)	
+	643(69)	152(77)	972(75)	
HER-2				0.832/<0.001
0/1+	696(75)	150(75)	1075(82)	
2+	159(17)	34(17)	168(13)	
3+	76(8)	15(8)	66(5)	

Characteristics	PSIMPC (n,%)	IMPC(n,%)	IBC-NST (n,%)	P^a/P^b
Local regional recurrence/Distant metastasis	193(26)	62(39)	189(19)	<0.001/<0.001
Death of tumor	93(12)	35(21)	57(6)	<0.001/<0.001

IMPC invasive micropapillary carcinoma, PSIMPC precursor state of IMPC, LN lymph node, LVI lymphovascular invasion, ER estrogen receptor, PR progesterone receptor, HER-2 human epidermal growth factor receptor 2, P^a and P^b represent the P value of PSIMPC compared with IMPC and IBC-NST respectively.

Table 2.

Correlation of the location PSIMPC with patient clinicopathologic characteristics

Characteristics	location of PSIMPC (n,%)			*P*
	both peripheral and internal group	peripheral only group	internal only group	
Age at diagnosis				0.787
≤50	275 (47)	71(50)	104(47)	
>50	308 (53)	70(50)	116(53)	
Tumor size (mm)				0.374
≤20	188 (33)	50(36)	72(33)	
20-50	343(59)	84(60)	132(61)	
> 50	46(8)	5(4)	12(6)	
PSIMPC proportion				<0.001
⩽25%	364 (62)	112(79)	170(77)	
26-50%	123(22)	11(8)	29(13)	
51-75%	60(11)	12(8)	15(7)	
76- 95%	30(5)	6(4)	6(3)	
LN				<0.001
−	223 (38)	56(40)	118(54)	
+	360 (62)	85(60)	102(46)	
LVI				<0.001
−	325(56)	94(67)	162(74)	
+	258(44)	47(33)	58(26)	
TNM stage				0.007
1	99(17)	22(16)	52 (24)	
2	265(46)	75(54)	114 (52)	
3/4	210(37)	42(30)	52(24)	
Histologic Grade				0.881
I	36(7)	7(6)	13(6)	
II	424(77)	104(81)	162(80)	
III	87(16)	17(13)	28(14)	
ER				0.005
−	166(29)	30(22)	40(19)	
+	401(71)	108 (78)	174(81)	
PR				0.006
−	195(34)	38(27)	50(23)	
+	373(66)	100 (73)	167(77)	
HER-2				0.024
0/1+	412(72)	102(73)	178(83)	
2+	103(18)	27(19)	28(13)	

Characteristics	location of PSIMPC (n,%)			*P*
	both peripheral and internal group	peripheral only group	internal only group	
3+	56(10)	11(8)	9(4)	
Local regional recurrence/Distant metastasis	123(27)	26(22)	43(25)	0.467
Death of tumor	62 (14)	9(10)	22(24)	0.236

PSIMPC precursor state of invasive micropapillary carcinoma, LN lymph node, LVI lymphovascular invasion, ER estrogen receptor, PR progesterone receptor, HER-2 human epidermal growth factor receptor 2,

Table 3.

The relationship between the proportion of PSIMPC and patient clinicopathological characteristics

Characteristics	PSIMPC proportion(n,%)				*P*
	⩽25%	26-50%	51-75%	76-100%	
Age at diagnosis					0.216
≤50	324 (50.0)	73(43.7)	37 (40.7)	19(44.2)	
> 50	324 (50.0)	94(56.3)	54 59.3)	24(55.8)	
Tumor size (mm)					0.668
≤20	214 (33.5)	57(34.3)	30(33.3)	9(21.4)	
20-50	382(59.8)	95(57.2)	54 (60.0)	31(73.8)	
> 50	43(6.7)	14(8.4)	6(6.7)	2(4.8)	
LN					0.911
−	269 (41.5)	74(44.3)	38(41.8)	17(39.5)	
+	379 (58.5)	93(55.7)	53 (58.2)	26(60.5)	
LVI					0.303
−	408(63.1)	92(55.1)	57 (62.6)	27(62.8)	
+	239(36.9	75(44.9)	34(37.4)	16(37.2)	
TNM stage					0.602
1	122(19.1)	34(20.6)	12(13.2)	5(11.9)	
2	314(49.2)	70(42.4)	49 (53.8)	22(52.4)	
3/4	202(31.7)	61(37.0)	30 (33.0)	15(35.7)	
Histologic Grade					0.756
I	41 (6.8)	7(4.5)	6(7.1)	2(5.3)	
II	471(77.7)	127(82.5)	63(74.1)	33(86.8)	
III	94 (15.5)	20(13.0)	16 (18.8)	3(7.9)	
ER					<0.001
−	141(22.4	43(26.1)	37(41.6)	18(43.9)	
+	488(77.6)	122(73.9)	52(58.4)	23(56.1)	
PR					<0.001
−	168(26.6)	56(33.7)	39(43.8)	22(52.4)	
+	463(73.4)	110(66.3)	50(56.2)	20(47.6)	
HER-2					<0.001
0/1+	494(78.0)	125(75.3)	55(60.4)	22(53.7)	
2+	94(14.8)	33(19.9)	20(2.0)	12(29.3)	
3+	45(7.1)	8(4.8)	16(17.6)	7(17.1)	
Local regional recurrence/Distant metastasis	132(25.8)	35(28.2)	19(25.7)	7(18.9)	0.731
Death of tumor	57(11.0)	17(13.5)	15(20.3)	4(10.8)	0.143

PSIMPC precursor state of invasive micropapillary carcinoma, LN lymph node, LVI lymphovascular invasion, ER estrogen receptor, PR progesterone receptor, HER-2 human epidermal growth factor receptor 2,

Table 4

Univariate and multivariate analyses of clinicopathologic features for prognosis of PSIMPC and IBC-NST

	Univariate			Multivariate		
	HR	**95 % CI**	***P***	**HR**	**95 % CI**	***P***
DFS						
Age at diagnosis	1.051	0.859-1.25	0.631	/	/	/
Tumor size	1.593	1.399-1.895	<0.001	1.366	1.141-1.635	0.001
Histologic Grade	1.194	0.950-1.501	0.129	/	/	/
LN	2.752	2.221-3.428	<0.001	2.286	1.809-2.888	<0.001
LVI	2.009	1.636-2.466	<0.001	1.428	1.146-1.778	0.001
ER	0.973	0.766-1.238	0.827	/	/	/
PR	0.829	0.662-1.036	0.100	/	/	/
HER-2	1.068	0.896-1.274	0.463	/	/	/
PSIMPC	1.458	1.193-1.782	<0.001	1.263	1.024-1.557	0.029
OS						
Age at diagnosis	1.353	0.981-1.867	0.065	/	/	/
Tumor size	2.407	1.837-30159	<0.001	1.584	1.169-2.147	0.003
Histologic Grade	2.248	1.582-3.193	<0.001	1.878	1.285-2.745	0.001
LN	4.675	3.099-7.053	<0.001	3.165	2.002-5.002	<0.001
LVI	3.022	2.190-4.169	<0.001	1.983	1.375-2.860	<0.001
ER	0.578	0.409-0.817	0.002	0.764	0.464-1.257	0.289
PR	0.626	0.446-0.880	0.007	0.843	0.526-1.351	0.478
HER-2	1.318	1.020-1.702	0.035	1.052	0.790-1.400	0.730
PSIMPC	2.194	1.577-3.053	<0.001	1.577	1.089-2.284	0.016

PSIMPC precursor state of invasive micropapillary carcinoma, LN lymph node, LVI lymphovascular invasion, ER estrogen receptor, PR progesterone receptor, HER-2 human epidermal growth factor receptor 2,

Table 5

Univariate and multivariate analyses of clinicopathologic features for prognosis of PSIMPC

	Univariate			Multivariate		
	HR	**95 % CI**	***P***	**HR**	**95 % CI**	***P***
DFS						
Age at diagnosis	1.059	0.825-1.453	0.529	/	/	/
Tumor size	1.904	1.485-2.440	<0.001	1.604	1.237-2.080	<0.001
Histologic Grade	1.123	0.809-1.558	0.488	/	/	/
LN	2.687	1.929-3.743	<0.001	2.238	1.587-3.156	<0.001
LVI	1.787	1.347-2.371	<0.001	1.493	1.120-1.991	0.006
ER	0.803	0.581-1.110	0.184	/	/	/
PR	0.746	0.552-1.009	0.057	/	/	/
HER-2	1.053	0.838-1.323	0.658	/	/	/
OS						
Age at diagnosis	1.578	1.043-2.388	0.031	1.637	1.052-2.549	0.029
Tumor size	2.991	2.109-4.241	<0.001	2.272	1.548-3.336	0.000
Histologic Grade	1.859	1.186-2.915	0.007	1.577	0.987-2.520	0.057
LN	4.733	2.631-8.513	<0.001	2.847	1.555-5.214	0.001
LVI	2.517	1.652-3.835	<0.001	1.950	1.237-3.075	0.004
ER	0.479	0.311-0.738	0.001	0.791	0.418-1.495	0.470
PR	0.544	0.358-0.829	0.005	0.842	0.461-1.537	0.575
HER-2	1.190	0.865-1.639	0.285	/	/	/

PSIMPC precursor state of invasive micropapillary carcinoma, LN lymph node, LVI lymphovascular invasion, ER estrogen receptor, PR progesterone receptor, HER-2 human epidermal growth factor receptor 2,