Breast Cancer Res Treat
DOI 10.1007/s10549-015-3413-4

EPIDEMIOLOGY

Invasive micropapillary mucinous carcinoma of the breast is associated with poor prognosis

Fangfang Liu[1] · Mu Yang[1] · Zhenhua Li[1] · Xiaojing Guo[1] · Yang Lin[1] · Ronggang Lang[1] · Beibei Shen[1] · Gordon Pringle[2] · Xinmin Zhang[2] · Li Fu[1]

Received: 29 April 2015 / Accepted: 2 May 2015

Abstract Invasive micropapillary carcinoma of breast (IMpC) is a special type of breast cancer with frequent lymph node metastasis (LNM) and poor prognosis, while pure mucinous carcinoma of breast (PMC) is generally associated with infrequent LNM and better prognosis. A similar micropapillary epithelial growth pattern has been described in PMC that was named as invasive micropapillary mucinous carcinoma (IMpMC), but its prognostic significance is as yet not known. A retrospective review of 531 cases of PMC in 43,685 cases of breast cancer diagnosed over a 10-year period was conducted to assess the frequency of IMpMC and its prognostic implications. IMpMC was identified in 134 (25.2 %) of the 531 PMC cases. Compared to conventional PMC (cPMC), IMpMC was found more frequently in younger patients and in tumors with increased frequency of LNM and lymphovascular invasion, and higher HER2 expression. In stage-matched Kaplan–Meier analysis, patients with stage II–III IMpMC suffered a decreased overall survival and recurrence-free survival (RFS) than matched cPMC patients. Multivariate analysis confirmed the presence of IMpMC morphology was an independent unfavorable predictor for LNM and RFS of PMC. However, decreased LNM, lower nuclear grade, higher expression of ER and PR, less expression of HER2, and better prognosis were identified in IMpMC when compared with IMpC ($n = 281$). This is the first study to show the prognostic significance of IMpMC in a large cohort. IMpMC pursues a more aggressive clinical course than cPMC and should be managed differently; therefore, recognition of IMpMC and its accurate diagnosis are clinically important.

Keywords Breast cancer · Mucinous carcinoma · Micropapillary carcinoma · Micropapillary mucinous carcinoma · Prognosis

Introduction

Studies of breast cancer have consistently demonstrated that invasive micropapillary carcinoma (IMpC) and pure mucinous carcinoma (PMC) are two opposite examples of breast cancer in terms of biologic behavior. IMpC is known for its proclivity for lymph node metastasis (LNM), early recurrence, and poor prognosis [1–3]. In contrast, PMC is believed to be indolent with infrequent LNM or recurrence, and a favorable prognosis [4–7]. A retrospective study of 11,422 cases of PMC confirmed the low regional LNM (12 %) and excellent survival (81 %) after 20 years of follow-up, compared to 36 % LNM at the time of surgery and 62 % survival at 20 years in patients with invasive ductal carcinoma of no special type [5].

Despite the remarkably different biologic behaviors, morphologic overlap between these two types of invasive breast carcinoma has been observed. IMpC with at least partial mucinous differentiation has been documented [3, 8] and a micropapillary epithelial growth pattern in PMC has also been reported in the literature [9, 10]. In 2002, Ng

Fangfang Liu and Mu Yang have contributed equally to this work.

✉ Li Fu
fuli@tijmu.edu.cn

[1] Department of Breast Pathology and Research Laboratory, Key Laboratory of Breast Cancer Prevention and Therapy (Ministry of Education), National Clinical Research Center for Cancer, Tianjin Medical University Cancer Institute and Hospital, Huanhuxi Road, Tianjin 300060, China

[2] Department of Pathology and Laboratory Medicine, Temple University Hospital, Philadelphia, PA, USA

Published online: 08 May 2015

described 5 of 21 cases of PMC with diffuse micropapillary architecture [9]. Since then, to our knowledge, only a limited number of such cases have been reported [9, 11–15]. The biologic behavior of PMC with a micropapillary growth pattern is unclear. Most of the studies, but not all [13], have indicated that the micropapillary growth pattern in PMC is associated with a higher rate of LNM and aggressive behavior, compared to PMC lacking micropapillary architecture (i.e., conventional PMC, cPMC). Because the pathogenetic relationship between the micropapillary subtype of PMC and IMpC is unclear, and to avoid potential confusion or misclassification, the micropapillary subset of PMC has been called invasive micropapillary mucinous carcinoma (IMpMC), micropapillary variant of mucinous carcinoma, or mucinous micropapillary carcinoma [9]. The first term is adopted in this report.

To date, the prognostic significance of IMpMC type of breast cancer has not been confirmed. We retrieved 531 cases of PMC from our archive that had been diagnosed in a 10-year period, and identified 134 cases of IMpMC within this group. The clinicopathological features of IMpMC were characterized and compared with cPMC and IMpC to determine the prognostic significance of micropapillary epithelial growth in breast cancer.

Materials and methods

Patient and tumors

Retrospective review of the archive of the Department of Pathology, Tianjin Medical University Cancer Hospital (Tianjin, China) identified 531 cases of PMC in 43,685 cases (1.2 %) of breast cancer that had been diagnosed over a 10-year period from 2003 to 2012. Carcinomas with signet-ring-cell differentiation were excluded from the study. All cases of PMC occurred in females with a median age of 53 years (range 23–88). The pathological tumor stage (TNM stage) was assessed according to the criteria established by the 6th edition of the American Joint Committee on Cancer (AJCC) staging manual. Patients received either mastectomy or lumpectomy, and all surgery included axillary lymph node dissection. Adjuvant therapy was offered to patients based on individual assessment of the clinicopathologic features of each tumor. The patients were followed up for 2–118 months, with a median of 60 months. The study was reviewed and approved by the Institutional Ethic Committee.

Morphological categorization and subclassification of the primary and metastatic lesions was assessed independently by two pathologists (LF and RL) blinded to the original diagnosis using the criteria of 2012 WHO classification of breast tumors. Cases with discordant diagnoses were reviewed by a third pathologist for consensus. IMpMC morphology is defined as a PMC containing a component with micropapillary architecture (Fig. 1). The growth pattern is similar to that in IMpC, with tumor cells showing an inside-out micropapillary arrangement revealed by the expression of surface glycoproteins (MUC1, EMA) on the cell surface facing the surrounding extracellular mucin. Other morphological features for IMpMC include"hobnail"cell morphology, frequent psammomatous calcifications, and micropapillary DCIS in the vicinity (Fig. 1). Micropapillary architecture constituted >50 % of the tumor epithelial components was required for a PMC to be diagnosed as IMpMC. In addition, 281 cases of IMpC diagnosed during the same time period were selected as the control group.

Representative tumor sections were immunostained with EMA (clone E29, DAKO, Denmark) and MUC1 (clone EPR1023, Abcam, UK). Immunohistochemistry for estrogen receptor (ER: clone SP1, Zymed, San Francisco, CA) and progesterone receptor (PR: clone SP2, Zymed) was re-evaluated using the 2010 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guideline [16]. Immunohistochemistry for human epidermal growth factor receptor 2 (HER2; DAKO HercepTestTM, Denmark) was re-evaluated using the 2014 ASCO/CAP updated guideline [17]. Fluorescence in situ hybridization (FISH) confirmation was performed using the PathVysion HER2 DNA probe kit following standard procedure in cases with equivocal immunohistochemical reaction. The assay was interpreted in accordance with the scoring criteria detailed in the 2014 ASCO/CAP updated guideline.

Statistical analysis

Statistical analysis was performed using SPSS 18.0 statistical software (SPSS, Chicago, IL). OS and RFS curves were drawn using Kaplan–Meier estimates and were compared using log-rank tests. Univariate and multivariate survival analyses were performed using Cox proportional hazards analysis. The clinical and biologic characteristics were compared between groups using Chi square test, the Mann–Whitney U test, and the Kruskal–Wallis test. Univariate and multivariate logistic regression models were applied to analyze the predictors for LN metastasis. All tests were two sides and a p value less than 0.05 was considered statistically significant.

Results

Clinicopathological characteristics

The clinicopathologic features of 134 cases of IMpMC, 397 cases of cPMC, and 281 cases of IMpC are

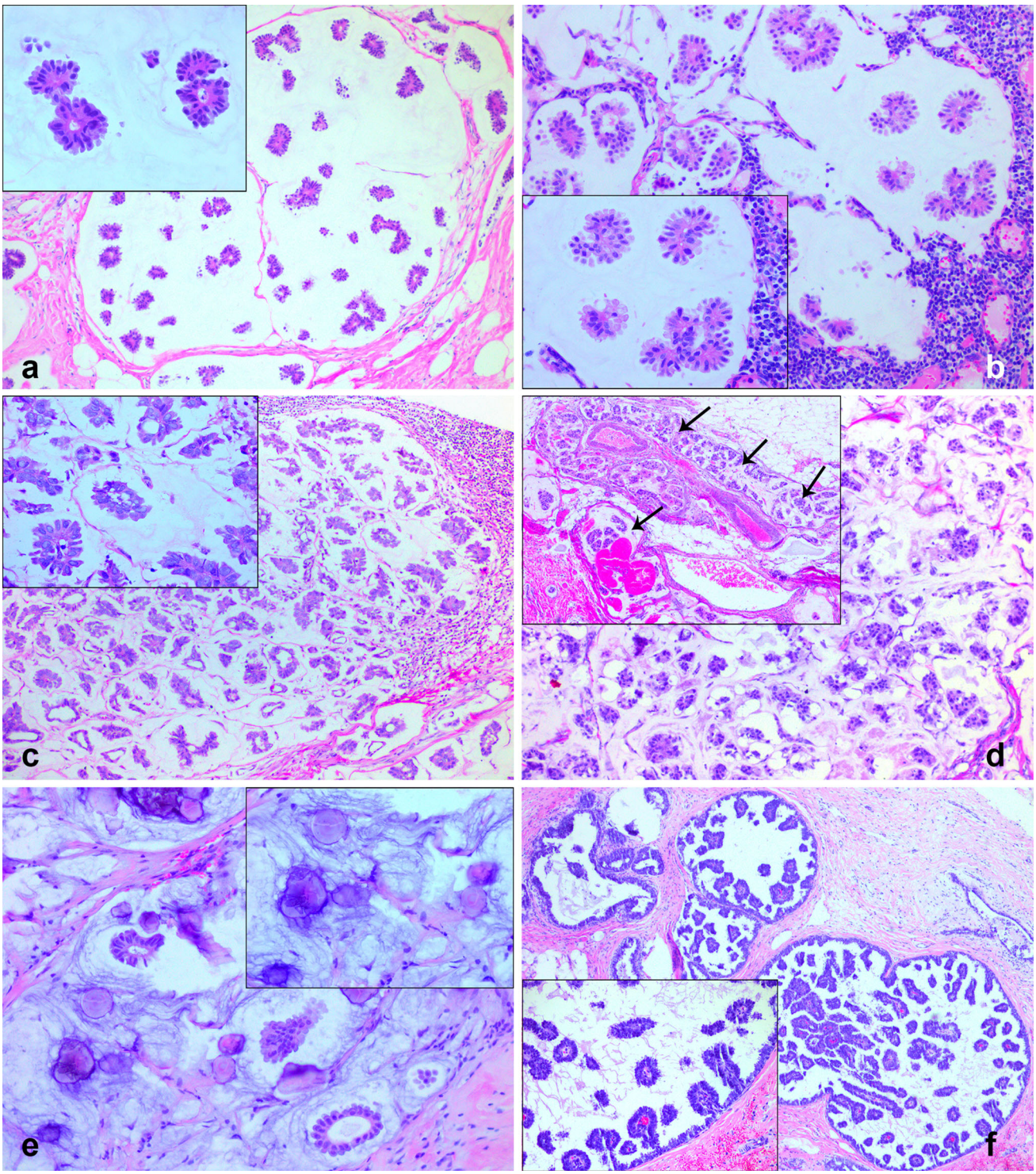

Fig. 1 Histologic features characteristic of IMpMC of the breast (hematoxylin and eosin stain). **a–e** Neoplastic cells are arranged in a pattern resembling IMpC within mucin-filled stromal compartments. **a–c** Floret-like and pseudoacinar structures and "hobnail"cells are commonly observed. **b** Lymph node metastases recapitulate features of the primary tumor IMpMC (**a**) with low nuclear grade. **c** Lymph node metastases of IMpMC with high nuclear grade. **d** Arrow denotes lymphatic invasion by tumor emboli. **e** Numerous psammomatous calcifications are observed that resemble IMpC. **f** Micropapillary DCIS, filled with mucin, in the vicinity of IMpMC. **a**, **c**, and **d** Original magnification ×10; **b** and **e** ×20; **f** and *inset* of **d** ×5; **a–c** and **e** *inset*, ×40

summarized in Table 1. Most of the IMpMCs presented with low nuclear grade (Grade 1; 75.4 %) and demonstrated the expression of ER (91.8 %) and PR (83.6 %). Compared to cPMC, IMpMC occurred in younger patients (median age, 46 vs. 57 years; $p < 0.001$), exhibited greater lymphovascular invasion (LVI; 23.9 vs. 2.5 %; $p < 0.001$), had a remarkably higher frequency of LNM (35.1 vs. 3.8 %; $p < 0.001$), had an increased number of lymph nodes with tumor metastasis per case (1.8 vs. 1.5; $p < 0.001$), exhibited greater HER2 overexpression or gene amplification (11.9 vs. 3.8 %; $p < 0.001$), exhibited higher risk for local and regional recurrence (5.2 vs. 0 %; $p < 0.001$) and distant metastasis (9 vs. 0.3 %; $p < 0.001$), and occurred in more patients who died of breast cancer (5.2 vs. 0 %; $p < 0.001$). Median tumor size, nuclear grade, and expression of ER and PR were not significantly different from those of cPMC ($p > 0.05$).

Compared to the 281 cases of IMpC, IMpMC demonstrated smaller tumor size (2.2 vs. 2.5 cm; $p = 0.002$), and less aggressive behavior as measured by decreased LNM (35.1 vs. 80.8 %; $p < 0.001$), decreased number of lymph nodes with metastasis per case (1.8 vs. 7.9; $p < 0.001$), less

Table 1 Patient information and clinicopathologic parameter comparisons

Clinicopathological parameters	IMpMC	cPMC		IMpC	
	n (%)	*n* (%)	p^a	*n* (%)	p^b
No. of patients	134 (25.2)	397 (74.8)		281	
Age, years					
Median (range)	46 (23–71)	57 (29–88)	<0.001	54 (30–80)	<0.001
Tumor size (cm)					
Median (range)	2.2 (0.8–11)	2.0 (0.4–11.5)	0.213	2.5 (0.2–18)	0.002
No. of LNs involved					
Mean ± SD (range)	1.8 ± 4.7 (0–34)	1.5 ± 1.8 (0–7)	<0.001	7.9 ± 9.7 (0–51)	<0.001
LN status					
pN0	87 (64.9)	382 (96.2)	<0.001	54 (19.2)	<0.001
pN1-3	47 (35.1)	15 (3.8)		227 (80.8)	
Definite LVI					
Negative	102 (76.1)	387 (97.5)	<0.001	48 (17.1)	<0.001
Positive	32 (23.9)	10 (2.5)		233 (82.9)	
Nuclear grade					
1	101 (75.4)	309 (77.8)	0.452	14 (5.0)	<0.001
2	28 (20.9)	86 (21.7)		221 (78.6)	
3	5 (3.7)	2 (0.5)		46 (16.4)	
ER positive	123 (91.8)	359 (90.4)	0.638	234 (83.3)	0.019
PR positive	112 (83.6)	322 (81.1)	0.522	208 (74.0)	0.030
HER2 OE/GA	16 (11.9)	15 (3.8)	<0.001	81 (28.8)	<0.001
Local regional recurrence	7 (5.2)	0 (0)	<0.001	34 (12.1)	0.028
Distant metastasis	12 (9.0)	1 (0.3)	<0.001	108 (38.4)	<0.001
Death of tumor	7 (5.2)	0 (0)	<0.001	30 (10.7)	0.068
Surgery					
Mastectomy	104 (77.6)	288 (72.5)	0.249	267 (95.0)	<0.001
Lumpectomy	30 (22.4)	109 (27.5)		14 (5.0)	
Chemotherapy					
Adjuvant	124 (92.5)	357 (89.9)	0.371	268 (95.4)	0.238
Neoadjuvant	11 (8.2)	16 (4.0)	0.057	84 (29.9)	<0.001
Radiotherapy	53 (39.6)	137 (34.5)	0.293	161 (57.3)	0.001
Endocrine therapy	126 (94.0)	364 (91.7)	0.380	246 (87.5)	0.063

IMpMC invasive micropapillary mucinous carcinoma, *cPMC* conventional pure mucinous carcinoma, *IMpC* invasive micropapillary carcinoma, p^a comparisons between IMpMC and cPMC, p^b comparisons between IMpMC and IMpC, *LN* lymph node, *LVI* lymphovascular invasion, *OE* HER2 overexpression, *GA* HER2 gene amplification

LVI (23.9 vs. 82.9 %; $p < 0.001$), lower nuclear grade ($p < 0.001$), increased expression of ER (91.8 vs. 83.3 %; $p = 0.019$) and PR (83.6 vs. 74 %; $p = 0.030$), lower HER2 overexpression or gene amplification (11.9 vs. 28.8 %; $p < 0.001$), and decreased local and regional recurrence (5.2 vs. 12.1 %; $p = 0.028$), and distant metastasis (9 vs. 38.4 %; $p < 0.001$). The study also found that fewer patients with IMpMC died of breast cancer than patients with IMpC; however the difference was not statistically significant (5.2 vs. 10.7 %; $p = 0.068$). IMpMC also occurred in younger patients than IMpC (median age, 46 vs. 54 years; $p < 0.001$).

The surgical and adjuvant managements of the breast cancer patients were summarized in Table 1. In this cohort, patients with IMpMC or cPMC were managed similarly. In contrast to IMpC, fewer patients with IMpMC received mastectomy ($p < 0.001$), neoadjuvant chemotherapy ($p < 0.001$), and adjuvant radiotherapy ($p = 0.001$), while a similar proportion of patients in the two group received adjuvant chemotherapy and endocrine therapy.

Lymph node metastasis and local recurrence of IMpMC

Thirty-three of 47 (33/47, 70.2 %) IMpMCs metastatic to lymph nodes manifested a micropapillary architecture similar to that observed in the primary tumor, but with a decreased amount of extracellular mucin. Eleven of the remaining cases (11/47, 23.4 %) showed a morphologic mixture of IMpC and IMpMC in different foci of metastasis, and metastatic carcinoma in the other 3 cases (3/47, 6.4 %) appeared as IMpC only, with complete loss of extracellular mucin. All seven cases with local and regional recurrence demonstrated tumor morphology of IMpC without mucin production identified.

The incidence of LNM in IMpMC was 9.2 times higher than that of cPMC (35.1 vs. 3.8 %, $p < 0.001$; Table 1). The odds of IMpMC occurring with LNM was nearly 11 times higher than that of cPMC using univariate analysis (OR = 10.87, $p < 0.001$) and nearly four times higher using multivariate analysis (OR = 3.65, $p = 0.005$). The IMpMC morphology was identified as an independent predictor for LNM in PMC by univariate and multivariate analyses (Table 2).

Prognostic associations

IMpMC was associated with decreased OS and RFS, compared to cPMC ($p = 0.001$; $p < 0.001$), but demonstrated a more favorable OS and RFS than IMpC ($p < 0.001$; $p < 0.001$) (Fig. 2). In a stage-matched analysis of OS and RFS, there were no statistically significant differences in OS or RFS between the patients with stage I IMpMC and stage I cPMC ($p > 0.05$; Fig. 3). Patients with stage II-III IMpMC had a decreased OS and RFS than patients with stage II–III cPMC ($p = 0.001$; $p < 0.001$; Fig. 3). Patients with IMpC always showed a worst outcome among the three groups after matching by TNM stage ($p < 0.05$; Fig. 3). In multivariate analysis, after adjusting for tumor size, grade, and lymph node status, the IMpMC morphology was proved to be independent negative prognostic factors for RFS of PMC (HR = 21.23, $p = 0.004$; Table 3). The association of the IMpMC morphology with OS was not proved to be significant by univariate analysis ($p = 0.176$; Table 3).

To identify the clinicopathologic factors affecting the prognosis of IMpMC patients, we used Cox regression analysis and found that younger age (HR = 0.18, $p = 0.023$), high LNM rate (HR = 6.03, $p < 0.001$), high nuclear grade (HR = 5.61, $p = 0.021$), and HER2 overexpression/gene amplification (HR = 1.80, $p = 0.048$; Table 4) were the independent predictors for unfavorable RFS. High LNM rate (HR = 3.16, $p < 0.001$), high nuclear grade (HR = 5.80, $p = 0.045$), and HER2 overexpression/gene amplification (HR = 2.62, $p = 0.043$; Table 4) were identified to be the independent predictors for unfavorable OS. Although tumor size was associated with patient's RFS and OS, it was not an independent predictor in this cohort (Table 4).

Discussion

PMC is an uncommon special type of carcinoma, accounting for 1–6 % of all breast malignancies [18]. It usually occurs in older patients and is considered an indolent tumor with a low rate of local and distant recurrence and excellent 5–19 year disease-free survival. Tumors with large quantity of extracellular mucin as observed at low power examination may harbor scattered small foci of tumor cells exhibiting a micropapillary architecture when observed at high power. The micropapillary architecture of the tumor cells is similar to that seen in IMpC with the characteristic inside-out cell arrangement highlighted by EMA and/or MUC1 immunohistochemistry [19].

This morphologic variant of PMC, referred to as IMpMC, is under-recognized in daily practice largely due to its unknown prognostic significance. Since the first description by Ng in 2002, the small number of published reports [9, 11–15], each relying on limited numbers of cases, suggests a 12–35 % incidence of IMpMC in PMC. The broad range may be attributed to the limited sample sizes, geographic location of patients, and more importantly by the lack of defined diagnostic criteria. We identified an incidence of 25.2 % (134/531) IMpMC in a large cohort of PMC diagnosed at our institution in a 10-year period. The reverse polarity of the micropapillary

Table 2 Univariate and multivariate analyses (logistic regression) for lymph node metastasis of PMC

Factors	Univariate			Multivariate		
	OR	95 % CI	*p*	OR	95 % CI	*p*
Age	0.95	0.93–0.97	<0.001	0.96	0.94–0.99	0.026
Tumor size	2.41	1.32–4.40	<0.001	1.29	1.08–1.55	0.005
LVI (negative vs. positive)	62.72	22.60–174.07	<0.001	20.62	6.10–69.73	<0.001
Nuclear grade (1 vs. 2 vs. 3)	2.90	1.76–4.78	<0.001	2.12	0.92–4.86	0.077
IMpMC morphology (no vs. yes)	10.87	5.52–21.28	<0.001	3.65	1.49–8.93	0.005

OR odds ratio, *95 % CI* 95 % confidence interval, *PMC* pure mucinous carcinoma, *LVI* lymphovascular invasion, *IMpMC* invasive micropapillary mucinous carcinoma

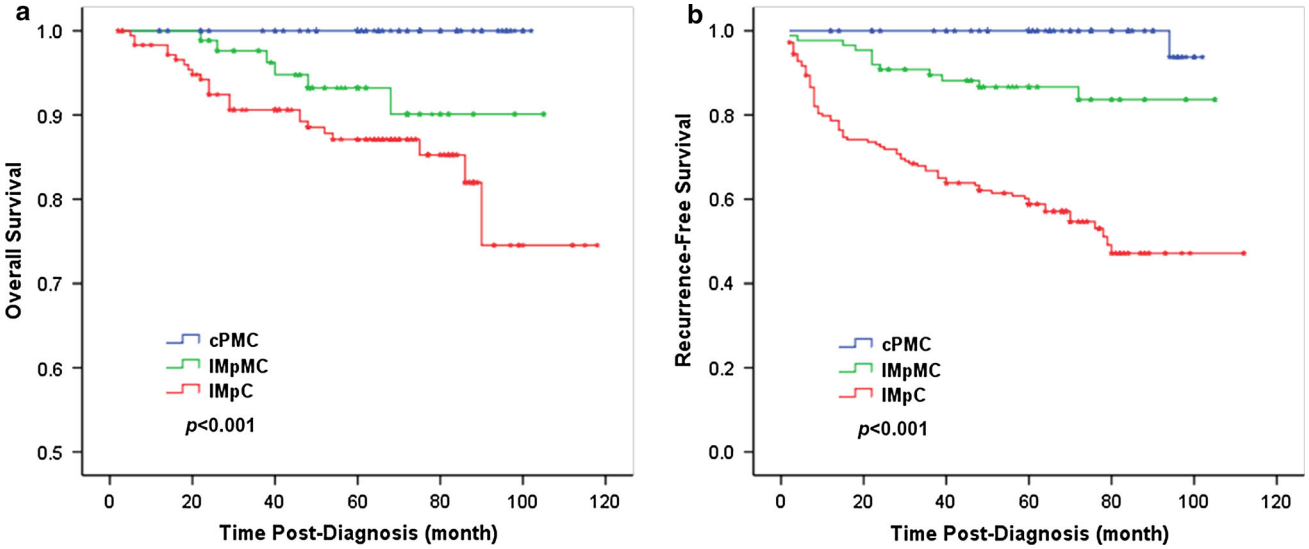

Fig. 2 Kaplan–Meier survival estimates according to the histologic types. IMpMC showed significantly decreased OS (**a**) and RFS (**b**) than cPMC. IMpC shows the worst OS (**a**) and RFS (**b**) among the three groups. *OS* overall survival, *RFS* recurrence-free survival

structures was confirmed in all the cases by MUC1 and EMA immunohistochemistry. However, we emphasized the presence of micropapillary architecture in making the diagnosis, as altered cell orientation identified by MUC1 and/or EMA staining patterns could be seen in tumor clusters in a large number of cPMCs and its alone is not the criteria for the diagnosis of IMpMC. In addition,"hobnail"cell morphology, frequent psammomatous calcifications, and a micropapillary DCIS in the vicinity were used as supporting evidence for the diagnosis [15]. Although currently there are no standard diagnostic criteria, a combination of these features could be employed to ensure a consistent and repeatable diagnosis of IMpMC until specific criteria are further defined. Unclassifiable cases with ambiguous features of IMpMC and IMpC, or with a mixed type of the two components certainly exist, but were not included in this study.

The underlying question is whether the presence of the diagnostic micropapillary architecture modifies the biologic characteristics of PMC. Most studies have linked IMpMC with increased LNM and aggressive behavior [9, 11–15], but conflicting results have been reported. Bal et al. [13] described 6 low-grade IMpMC cases with no LNM and concluded an indolent behavior. In the current study, IMpMC was demonstrated a significantly increased LVI and LNM, and decreased OS and RFS than cPMC. Multivariate analysis confirmed it as an independent unfavorable predictor for RFS of PMC. Our findings, by stage-matched analysis, illustrate that the poorer prognosis of IMpMC was mainly due to the contribution of stage II–III patients, but not the low stage cases. When compared to IMpC, patients with IMpMC were shown to have a better prognosis irrespective of tumor stage. These results indicate that IMpMC exhibits a level of aggressiveness intermediate between cPMC and IMpC. IMpC has been considered as an aggressive subtype of breast cancer and therefore has been managed more aggressively for years. In our study, more IMpC patients received mastectomy

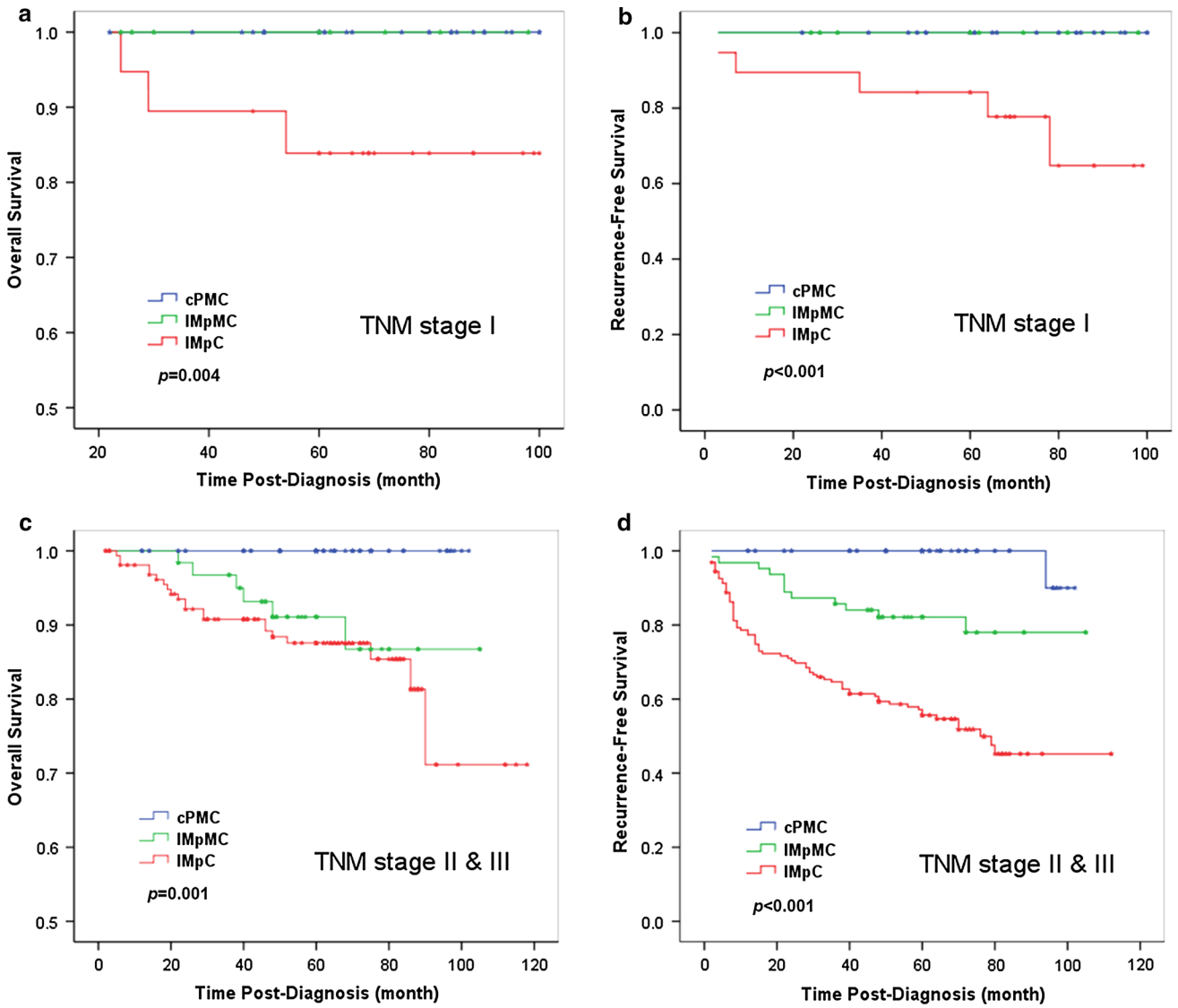

Fig. 3 Stage-matched Kaplan–Meier survival estimates according to the histologic types. In TNM stage I cases, no statistically significant differences were shown in OS (**a**) or RFS (**b**) between IMpMC and cPMC. In TNM stage II–III cases, patients with IMpMC had a significantly decreased OS (**c**) and RFS (**d**) than cPMC. IMpC showed a worst OS (**a**, **c**) and RFS (**b**, **d**) among the three groups in stages I and II–III. *OS* overall survival, *RFS* recurrence-free survival

instead of lumpectomy, neoadjuvant chemotherapy, and adjuvant radiotherapy than IMpMC. In contrast, no significant difference was observed in surgery or adjuvant management between the patients with IMpMC and cPMC. Our findings suggest that relatively more aggressive treatments should be considered in IMpMC management, especially in patients with stage locally advanced cancer.

LNM is an important indicator for unfavorable prognosis of breast cancer patients, including those with PMC [5]. Axillary LNM for IMpMC occurs in 20–43 % of patients [9, 11, 14, 15], significantly higher than the average rate of 12 % for PMC patients overall. We identified a ninefold increase in LNM rate and a fourfold increase in the odds of LNM in IMpMC by multivariate analysis in contrast to cPMC. IMpMC morphology was identified as an independent predictor for LNM of PMC. Because of the indolent behavior of PMC, axillary staging in surgical intervention is even not suggested [20]. Our results suggest that axillary staging by sentinel lymph node biopsy or axillary lymph node dissection should be considered for patients with IMpMC due to its highly increased LNM rate.

Morphologically, IMpMC shares features with both PMC and IMpC, and this dual phenotype may govern its intermediate clinical behavior. Abundant extracellular mucin has been suggested to be an obstacle to lymphovascular invasion and LNM in PMC [3]. Examination of the LNMs in IMpMC cases found that mucin around the micropapillary clusters tended to decrease, or was

Table 3 Univariate and multivariate analyses of clinicopathologic features for prognosis of PMC

Factors	Univariate			Multivariate		
	HR	95 % CI	*p*	HR	95 % CI	*p*
RFS						
Age	0.97	0.93–1.02	0.195	–	–	–
Tumor size	1.40	1.12–1.73	0.003	1.84	1.11–3.04	0.019
LN status (negative vs. positive)	3.95	1.20–13.00	0.024	7.48	2.99–18.69	<0.001
Nuclear grade (1 vs. 2 vs. 3)	3.36	1.27–8.86	0.014	3.34	1.58–7.05	0.002
IMpMC morphology (no vs. yes)	23.35	3.03–179.81	0.002	21.23	2.67–168.76	0.004
OS						
Age	0.97	0.90–1.04	0.363	–	–	–
Tumor size	2.87	0.64–12.96	0.169	–	–	–
LN status (negative vs. positive)	5.06	2.64–9.70	<0.001	11.87	3.96–35.56	<0.001
Nuclear grade (1 vs. 2 vs.3)	10.52	1.93–58.8	0.007	11.88	1.57–9.89	0.017
IMpMC morphology (no vs. yes)	164.9	0.10–2.70E5	0.176	–	–	–

HR hazard ratio, *95 % CI* 95 % confidence interval, *PMC* pure mucinous carcinoma, *IMpMC* invasive micropapillary mucinous carcinoma, *LN* lymph node, *OE* HER2 overexpression, *GA* HER2 gene amplification

Table 4 Univariate and multivariate analyses of clinicopathologic features for prognosis of IMpMC

Factors	Univariate			Multivariate		
	HR	95 % CI	*p*	HR	95 % CI	*p*
PFS						
Age	0.28	0.08–0.98	0.046	0.18	0.04–0.78	0.023
Tumor size	6.67	1.39–32.14	0.018	3.62	0.74–17.60	0.111
LN status (negative vs. positive)	2.12	1.25–3.59	0.006	6.03	2.84–12.82	<0.001
Nuclear grade (1 vs. 2 vs. 3)	2.33	1.40–3.85	0.001	5.61	1.30–24.27	0.021
HER2 OE/GA (no vs. yes)	2.03	1.30–3.18	0.002	1.80	1.01–3.21	0.048
OS						
Age	1.04	0.95–1.13	0.423	–	–	–
Tumor size	2.79	1.44–5.38	0.002	2.95	0.36–24.34	0.315
LN status (negative vs. positive)	3.46	1.75–6.81	<0.001	3.16	1.75–5.68	<0.001
Nuclear grade (1 vs. 2 vs. 3)	6.24	1.14–34.21	0.035	5.80	1.04–32.43	0.045
HER2 OE/GA (no vs. yes)	2.69	1.07–6.77	0.036	2.62	1.03–6.67	0.043

HR hazard ratio, *95 % CI* 95 % confidence interval, *IMpMC* invasive micropapillary mucinous carcinoma. *LN* lymph node, *OE* HER2 overexpression, *GA* HER2 gene amplification

completely lost, producing an IMpC-type metastasis. Mucinous carcinomas giving rise to non-mucinous LNM have been reported previously [21]. Some investigators have offered the explanation that sampling error of the primary tumor misses the non-mucinous micropapillary component. However, others believe that the development of aggressive clones by positive selection within the tumor results in metastasis and the loss of mucin production and secretion [21]. The latter provides a reasonable explanation for our observation that local and regional recurrence of IMpMC totally presented with the morphology of IMpC, and it is our belief that transformation to IMpC with loss of mucin is a major pathogenetic event leading to late recurrence and decreased patent survival. This suggests that IMpMC and IMpC form a spectrum of the same tumor, differing in the amount of extracellular mucin. Additional molecular studies may be able to clarify the genetic and transcriptomic relationship between cPMC, IMpMC, and IMpC.

In addition, some researchers have reported IMpMC tends to occur in young patients (median age, 44–55 years) [9, 13, 14]. Our study demonstrated that IMpMC occurs with a median age (46 years) approximately a decade younger than cPMC, and that the younger age is an independent predictor for decreased RFS of IMpMC. Consistent with previous transcriptomic studies of PMC [22–24], most of our IMpMC cases can be classified as luminal

subtypes due the prevalent expression of ER, PR, and low expression of HER-2. However, HER2 expression was found in a significantly higher proportion of IMpMC than cPMC, in agreement with earlier studies [9, 14, 15]. HER2 status was confirmed to be an independent predictor for unfavorable RFS and OS of patients with IMpMC.

In conclusion, this study is the first to show the prognostic significance of IMpMC in a large cohort of patients. Our results offer an explanation for the heterogeneity in biologic behavior of PMC. IMpMC is identified as a subset of mucin-producing breast carcinomas with biologic behavior between cPMC and IMpC. These tumors may represent different points in a spectrum of the same subgroup of breast cancer. Additional studies to clarify the pathogenetic relationship between these tumors are required which could lead to a more accurate classification and better stratification of tumors for appropriate patient management. Sentinel lymph node biopsy and/or axillary lymph node dissection followed by more aggressive postoperative therapy should be considered for patients with IMpMC. Therefore, recognition of IMpMC and its accurate diagnosis are clinically important.

Acknowledgments Research supported by grants from the National Natural Science Foundation of China (Grant No. 81202101, 81172531, and 30930038).

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard The experiments comply with the current laws.

References

1. Tavassoli FDP (2003) World Health Organization classification of tumours. IARC Press, Lyon
2. Pettinato G, Manivel CJ, Panico L, Sparano L, Petrella G (2004) Invasive micropapillary carcinoma of the breast: clinicopathologic study of 62 cases of a poorly recognized variant with highly aggressive behavior. Am J Clin Pathol 121(6):857–866
3. Walsh MM, Bleiweiss IJ (2001) Invasive micropapillary carcinoma of the breast: eighty cases of an underrecognized entity. Hum Pathol 32(6):583–589
4. Barkley CR, Ligibel JA, Wong JS, Lipsitz S, Smith BL, Golshan M (2008) Mucinous breast carcinoma: a large contemporary series. Am J Surg 196(4):549–551
5. Di Saverio S, Gutierrez J, Avisar E (2008) A retrospective review with long term follow up of 11,400 cases of pure mucinous breast carcinoma. Breast Cancer Res Treat 111(3):541–547
6. Diab SG, Clark GM, Osborne CK, Libby A, Allred DC, Elledge RM (1999) Tumor characteristics and clinical outcome of tubular and mucinous breast carcinomas. J Clin Oncol 17(5):1442–1448
7. Louwman MW, Vriezen M, van Beek MW, Nolthenius-Puylaert MC, van der Sangen MJ, Roumen RM, Kiemeney LA, Coebergh JW (2007) Uncommon breast tumors in perspective: incidence, treatment and survival in the Netherlands. Int J Cancer 121(1): 127–135
8. Luna-More S, Casquero S, Perez-Mellado A, Rius F, Weill B, Gornemann I (2000) Importance of estrogen receptors for the behavior of invasive micropapillary carcinoma of the breast. Review of 68 cases with follow-up of 54. Pathol Res Pract 196(1):35–39
9. Ng WK (2002) Fine-needle aspiration cytology findings of an uncommon micropapillary variant of pure mucinous carcinoma of the breast: review of patients over an 8-year period. Cancer 96(5):280–288
10. Akiyoshi T, Nagaie T, Tokunaga M, Tajima M, Morita M, Nakatsuka A, Taga S, Wakiyama S, Ikebe M, Nakanishi K et al (2003) Invasive micropapillary carcinoma of the breast with minimal regional lymph node metastasis regardless of the huge size: report of a case. Breast Cancer 10(4):356–360
11. Madur B, Shet T, Chinoy R (2007) Cytologic findings in infiltrating micropapillary carcinoma and mucinous carcinomas with micropapillary pattern. Acta Cytol 51(1):25–32
12. Shet T, Chinoy R (2008) Presence of a micropapillary pattern in mucinous carcinomas of the breast and its impact on the clinical behavior. Breast J 14(5):412–420
13. Bal A, Joshi K, Sharma SC, Das A, Verma A, Wig JD (2008) Prognostic significance of micropapillary pattern in pure mucinous carcinoma of the breast. Int J Surg Pathol 16(3):251–256
14. Ranade A, Batra R, Sandhu G, Chitale RA, Balderacchi J (2010) Clinicopathological evaluation of 100 cases of mucinous carcinoma of breast with emphasis on axillary staging and special reference to a micropapillary pattern. J Clin Pathol 63(12):1043–1047
15. Barbashina V, Corben AD, Akram M, Vallejo C, Tan LK (2013) Mucinous micropapillary carcinoma of the breast: an aggressive counterpart to conventional pure mucinous tumors. Hum Pathol 44(8):1577–1585
16. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M et al (2010) American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. Arch Pathol Lab Med 134(6):907–922
17. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, Allred DC, Bartlett JM, Bilous M, Fitzgibbons P et al (2014) 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. Arch Pathol Lab Med 138(2):241–256
18. Andre S, Cunha F, Bernardo M, Meneses J, Sousa E, Cortez F, Soares J (1995) Mucinous carcinoma of the breast: a pathologic study of 82 cases. J Surg Oncol 58(3):162–167
19. Nassar H, Pansare V, Zhang H, Che M, Sakr W, Ali-Fehmi R, Grignon D, Sarkar F, Cheng J, Adsay V (2004) Pathogenesis of invasive micropapillary carcinoma: role of MUC1 glycoprotein. Mod Pathol 17(9):1045–1050
20. Paramo JC, Wilson C, Velarde D, Giraldo J, Poppiti RJ, Mesko TW (2002) Pure mucinous carcinoma of the breast: is axillary staging necessary? Ann Surg Oncol 9(2):161–164
21. Rasmussen BB, Rose C, Christensen IB (1987) Prognostic factors in primary mucinous breast carcinoma. Am J Clin Pathol 87(2):155–160
22. Weigelt B, Horlings HM, Kreike B, Hayes MM, Hauptmann M, Wessels LF, de Jong D, Van de Vijver MJ, Van't Veer LJ, Peterse JL (2008) Refinement of breast cancer classification by molecular characterization of histological special types. J Pathol 216(2): 141–150
23. Weigelt B, Reis-Filho JS (2009) Histological and molecular types of breast cancer: is there a unifying taxonomy? Nat Rev Clin Oncol 6(12):718–730
24. Weigelt B, Mackay A, A'Hern R, Natrajan R, Tan DS, Dowsett M, Ashworth A, Reis-Filho JS (2010) Breast cancer molecular profiling with single sample predictors: a retrospective analysis. Lancet Oncol 11(4):339–349