The clinicopathological and prognostic characteristics of mucinous micropapillary carcinoma of the breast

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Research

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Abstract

Background

Mucinous micropapillary carcinoma (MMPC) is a unique subtype of breast cancer and detailed investigation of clinical characteristics of MMPC is not fully investigated.

Methods

MMPC, pure mucinous breast carcinoma (PMBC) and invasive micropapollary carcinoma (IMPC) samples were enrolled simultaneously and performed immunohistochemistry (IHC) analysis to explore the clinicopathological attributes of MMPC. Moreover, survival analysis of MMPC were performed among MMPC, PMBC and IMPC group and within MMPC group.

Results

The result showed that MMPC demonstrated distinct pathological features and vascular invasion, lymph node metastasis were two significant clinical attributes of MMPC. MMPC encountered a decreased survival time than PMBC but an increased survival time than IMBC while TNM stage and lymph node metastasis were identified as two independent prognostic elements for DFS of MMPC prognosis.

Conclusions

The data implied that further understanding and classification of MMPC may provide better individualized therapeutic strategies for MMPC treatment.

Background

Breast cancer is the most common cancer among the female worldwide [1]. Further understanding the histological heterogeneity is of great importance for the diagnosis and treatment of breast cancer. Mucinous carcinoma (MC) is a rare and special subtype of breast cancer with favorable prognosis and described as “clusters of generally small and uniform cells floating in large amounts of extracellular mucin” according to WHO breast tumor classification (2012) [2, 3]. Traditionally, MC of the breast consists of 2 subtypes based on the composition of MC component in the total tumor volume: pure mucinous breast carcinoma (PMBC, composed of > 90% mucinous component in the tumor) and mixed mucinous breast carcinoma [4, 5].

Early in 2002, Wai-Kuen Ng firstly introduced PMBC with a micropapillary shape consisting of morula-like clusters dangled in tight mucin pools, which was identified as a new subtype of PMBC and designated as mucinous micropapillary carcinoma (MMPC) [6]. However, some studies illustrated that the arrangement

of MMPC was analogous to that of invasive micropapollary carcinoma (IMPC). Moreover, MMPC also tended to show aggressive tumor behaviors, including lymph node metastasis and lymphovascular invasion. So MMPC should be categorized as the subtype of IMPC [7, 8]. Because the uncommonness of MMPC cases in clinical field, the classification of MMPC was still controversial.

In this present study, we enrolled MMPC, PMBC and IMPC samples and explored the clinicopathological characteristics of MMPC especially the prognostic factors, both among-group and within-group.

Methods

Sample collection

40 cases of MMPC were collected from the Department of Pathology of the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University from January 2010 to December 2018. Simultaneously, 90 cases of PMBC and 60 cases of IMPC were enrolled as control groups. Important clinicopathologic parameters including age, menstrual status, tumor size, ultrasound and molybdenum target data, LVI, LNM, ER, PR, HER2, Ki-67 status and TNM stage were collected. Moreover, various therapeutic strategies such as surgical style, adjuvant chemotherapy, radiation therapy, endocrine therapy, trastuzumab therapy were also recorded. BC was diagnosed and classified according to the American Joint Committee on Cancer (AJCC)/International Union against Cancer (UICC) tumor-node-metastasis (TNM) staging system. The discordant diagnosis of MMPC were reviewed by three pathologists independently using slides immunostained with EMA and MUC1 for consensus [9]. All cases were carefully followed up for 2–118 months, with a median of 60 months. Written informed consent was acquired from each patient in this study and the study protocol was approved by the Human Research Ethics Committee of the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University ([2019]KY083-01).

Immunohistochemistry (IHC) analysis

All tissue wax blocks were fixed with 10% formalin, cut into 4-μm sections, deparaffinized and rehydrated through graded alcohols. Endogenous peroxidase activity was blocked by incubation in 3% H_2O_2. Antigen retrieval was performed with citrate buffer and microwave heat induction. IHC analysis was conducted as previously described [10, 11]. All antibodies used for IHC assay were listed in Table 1. Positive ER/PR staining was defined as ≥ 1% cell nuclear staining, positive HER2 stainin was defined as ≥ 3 + cell membrane staining or ≥ 1 + fluorescence in situ hybridization (FISH, PathVysion HER2 DNA probe kit). High proliferation index Ki-67 was defined as ≥ 14% cell nuclear staining. Positive staining of neuroendocrine marker Syn, mucin marker MUC2 as well as EMA and MUC1 was defined as ≥ 10% cell cytoplasm staining.

Table 1
Antibody details for IHC analysis

Marker	Information
ER	Zhongshan Golden Bridge Biotechnology (Beijing, China), 1:1000
PR	Zhongshan Golden Bridge Biotechnology (Beijing, China), 1:1000
HER-2	Roche (Basel, Switzerland), 1:1000
Ki-67	MXB Biotechnology (Fuzhou, China), 1:1000
EMA	MXB Biotechnology (Fuzhou, China), 1:1000
MUC1	MXB Biotechnology (Fuzhou, China), 1:1000
MUC2	Zhongshan Golden Bridge Biotechnology (Beijing, China), 1:1000
Syn	Zhongshan Golden Bridge Biotechnology (Beijing, China), 1:1000
CgA	Zhongshan Golden Bridge Biotechnology (Beijing, China), 1:1000

Pathological diagnosis of MMPC

The pathological diagnosis of MMPC must meet the following items concurrently: 1. tumor cells are arranged in micropapillary type, pseudo-glandular type, and solid cell-mass cluster type; 2. mucus fills the contraction spaces around tumor cells; 3. mucus component accounts for 30%-90% of the total tumor volume; 4. EMA/MUC1 shows “inside-out” staining pattern [12, 13].

Statistical analysis

The data are expressed as the mean ± standard deviation. Differences between two groups were statistically analyzed using Student’s t-test. The variables between groups were evaluated using χ^2 tests or fisher's exact test. Overall survival (OS) and disease-free survival (DFS) curves were drawn using the Kaplan-Meier methods and were compared by log-rank tests. Univariate and multivariate Cox regression model were employed to identify the prognostic elements. For all tests, the significance level for statistical analysis was set at $p < 0.05$. All data were analyzed using the SPSS 23.0 (SPSS Inc, Chicago, IL, USA) and STATA 16.0 (Stata Corporation, College Station, TX, USA).

Results

Histological morphology of MMPC

MMPC contains a large amount of extracellular mucus (35%-90%). Tumor cells float in the mucous pool in the form of avascular axis with micropapillae, morula or rosette type and cubic or columnar cytoplasm are substantial. Representative micropapillae of MMPC could be characterized by a solid cluster or ring

arrangement of tumor cells separated by empty space, and demonstrated an “inside-out pattern”, which can be stained by EMA or MUC1 (Fig. 1).

Clinicopathologic information of MMPC patients

A total of 40 MMPC samples were collected from women and the principal clinical data are summarized in Table 2. The mean age of all patients was 56.2 years and the average tumor diameter was 1.9cm (1.0-4.5 cm). 6 cases have family history of malignancy (BC or other tumors). There were 6 cases before menopause and 34 cases after menopause. Bursting pain during menstruation was noted in 29 patients, and BI-RADS 4–6 level was witnessed in 32 cases by ultrasound and molybdenum target test. 30 patients were performed breast-conserving surgery and 10 were conducted modified radical mastectomy. Positive lymph node metastasis and vascular tumor thrombus were observed in 12 and 15 cases respectively. The number of positive expression of ER, PR, HER2 and Ki-67 was 34, 32, 5 and 10. Molecular classifications were as follows: 24 cases were Luminal A, 10 cases were Luminal B, 3 cases were Her2-enriched, 3 cases were basal. Positive Syn and MUC2 stainging were witnessed in 16 and 23 cases respectively. All 40 patients received postoperative chemotherapy (taxol + platinum), 32 received endocrinotherapy, 12 received radiotherapy while 4 received herceptin therapy. Among all the cases, 14 patients suffered tumor progression with lymph nodes metastasis to the ipsilateral chest wall, ipsilateral axillary and supraclavicular. For TNM stage, 25 patients were in stages I–II while the other 15 patients were in advanced stages III–IV.

Table 2
Comparison of clinicopathological features of MMPC, IMPC and PMBC

Clinicopathological factors	MMPC(n = 40)	PMBC(n = 90)	P	MMPC(n = 40)	IMPC(n = 60)	P
Age (years)			0.565			0.190
≥ 50	27	61		27	34	
50	13	29		13	26	
Family history			0.228			0.422
Yes	6	8		6	7	
No	34	82		34	53	
Menstrual state			0.107			0.033*
Postmenopausal	34	66		34	40	
Premenopausal	6	24		6	20	
Ultrasound (BI-RADS grading)			0.001*			0.195
Grade 1–3	8	42		8	7	
Grade 4–6	32	43		32	53	
Molybdenum target (BI-RADS classification)			0.111			0.195
Grade 1–3	8	29		8	7	
Grade 4–6	32	61		32	53	
Adjuvant chemotherapy			0.001*			0.212
Yes	40	72		40	57	
No	0	18		0	3	
Endocrine therapy			0.199			0.524
Yes	32	64		32	47	
No	8	26		8	13	
Herceptin therapy			0.031*			0.341
Yes	4	16		4	9	
No	36	74		36	51	

*p < 0.05

Clinicopathological factors	MMPC(n = 40)	PMBC(n = 90)	P	MMPC(n = 40)	IMPC(n = 60)	P
Radiotherapy			0.219			0.002*
Yes	5	6		5	21	
No	35	84		35	39	
Operation mode			0.512			0.048*
Breast conserving surgery	30	66		30	34	
Modified radical mastectomy	10	24		10	26	
Tumor diameter			0.023*			0.266
≥ 2cm	22	31		22	38	
2cm	18	59		18	22	
TNM staging			0.074			0.194
Stage I - II	25	69		25	31	
Stage I - II	15	21		15	29	
Vascular invasion			0.006*			0.012*
Yes	12	9		12	33	
No	28	81		28	27	
Lymph node metastasis			0.001*			0.047*
Yes	15	11		15	34	
No	25	79		25	26	
Neuroendocrine markers (Syn)			0.016*			0.518
Positive	16	18		16	25	
Negative	24	72		24	35	
Mucin labeling (MUC2)			0.118			0.001*
Positive	23	63		23	6	
Negative	17	27		17	54	
Molecular type			0.076			0.001*

*p < 0.05

Clinicopathological factors	MMPC(n = 40)	PMBC(n = 90)	P	MMPC(n = 40)	IMPC(n = 60)	P
Luminal A	24	55		24	13	
Luminal B	10	32		10	31	
HER-2 overexpression	3	2		3	9	
Triple negative	3	1		3	7	
ER expression			0.498			0.287
Positive	34	78		34	47	
Negative	6	12		6	13	
PR expression			0.486			0.019*
Positive	32	70		32	35	
Negative	8	20		8	25	
HER-2 expression			0.058			0.242
0–2+	35	87		35	48	
3 + or FISH+	5	3		5	12	
Ki-67 expression			0.072			0.001*
≥ 14%	10	36		10	43	
14%	30	54		30	17	
*p < 0.05						

Comparison of clinicopathological parameters among MMPC, PMBC and IMPC

As is shown in Table 2, several characteristics showed significant differences among MMPC, PMBC and IMPC. For comparison between MMPC and PMBC, important factors included ultrasound grade, tumor diameter, vascular invasion, lymph node metastasis and status of Syn. For comparison between MMPC and IMBC, critical attributes included menstruation status, vascular invasion, lymph node metastasis, status of MUC2, molecular type, PR and Ki-67 status. Specifically, vascular invasion, lymph node metastasis were two collective parameters when comparing MMPC, PMBC and IMPC (Table 2).

Survival analysis of MMPC

For comparison among groups, the 1-year, 3-year and 5- year DFS rates of MMPC, PMBC and IMPC were 100% vs 100% vs 100%,87% vs 100% vs 78%62% vs 99% vs 57%, while the related 1-year, 3-year and 5-year OS rates were100% vs 100% vs 100%95% vs 100% vs 90%78% vs 100% vs 85%. MMPC patients had a decreased survival time than PMBC patients but an increased survival time than IMBC patients

(Fig. 2). For comparison within MMPC groups for DFS, univariate analysis revealed that tumor diameter, TNM stage, vascular invasion, lymph node metastasis, molecular type, status of Ki-67 and Syn could significantly affect MMPC prognosis. Multivariate analysis further confirmed that TNM stage and lymph node metastasis may serve as independent prognostic factors for DFS of MMPC prognosis (Table 3, Table 4, Fig. 3).

Table 3
Univariate analysis of prognostic factors in MMPC for disease-free survival (DFS)

Parameters	HR	95% CI	P value
Age (years)	0.801	0.340–3.001	0.971
< 50 vs ≥ 50			
Family history	0.114	0.002–2.154	0.710
Yes vs No			
Menstrual state	0.321	0.019–3.101	0.812
Postmenopausal vs Premenopausal			
Ultrasound (BI-RADS grading)	3.630	0.123–1.689	0.096
Grade 4–6 vs Grade 1–3			
Molybdenum target (BI-RADS classification)	3.425	0.173–2.046	0.071
Grade 4–6 vs Grade 1–3			
Adjuvant chemotherapy	0.362	0.025–3.669	0.968
Positive vs Negative			
Radiotherapy	1.701	0.641–6.661	0.095
Positive vs Negative			
Endocrine therapy	0.340	0.056–2.154	0.562
Positive vs Negative			
Herceptin therapy	1.256	0.684–10.326	0.894
Negative vs Positive			
Tumor diameter	17.620	2.697–44.385	< 0.001*
≥ 2cm vs < 2cm			
TNM stage	28.160	1.621–54.361	< 0.001*
Stage III-IV vs I-II			
Vascular invasion	11.365	3.691–30.156	< 0.001*
Positive vs Negative			
Lymph node metastasis	14.700	6.069–22.124	< 0.001*
*p < 0.05			

Parameters	HR	95% CI	P value
Positive vs Negative			
Molecular type Luminal A vs Luminal B HER-2 overexpression vs Triple negative	12.756	6.125–61.578	< 0.001*
ER	0.140	0.001–6.458	0.710
Positive vs Negative			
PR	0.364	0.201–6.142	0.698
Positive vs Negative			
HER-2	0.669	0.125–3.458	0.712
0–2 + vs 3+/Fish+			
Neuroendocrine markers (Syn)	5.290	0.175–12.321	0.021*
Positive vs Negative			
Mucin labeling (MUC2)	0.189	0.001–11.025	0.622
Positive vs Negative			
Ki-67	26.32	9.187–55.325	< 0.001*
≥ 14% vs < 14%			
*p < 0.05			

Table 4
Multivariate analysis of prognostic factors in MMPC for disease-free survival (DFS)

Parameters	95% CI	P value
Tumor diameter ≥ 2cm vs < 2cm	0.643–5.884	0.275
TNM stage Stage III-IV vs I-II	6.083-515.402	0.030*
Vascular invasion Positive vs Negative	0.379–10.761	0.728
Lymph node metastasis Positive vs Negative	1.154–17.298	0.038*
Molecular typing Luminal A vs Luminal B HER-2 overexpression vs Triple negative	0.728–4.442	0.447
Neuroendocrine markers (Syn) Positive vs Negative	0.850-27.533	0.076
Ki-67 ≥ 14% vs < 14%	0.687–38.597	0.926
*p < 0.05		

Discussion

Due to the small number of MMPC cases and most of them are hidden in PMBC, clinicians and pathologists are far from aware of this type of special breast cancer. The incidence of PMBC of breast is low, accounting for 1%-4% of invasive breast cancer. PMBC is more common in elderly women and the median age of women at the time of PMBC diagnosis is 60 years. As for IMPC, the incidence rate is 1%-8.4%, and the median age of diagnosis is 50 years old. In comparison, the incidence of MMPC is lower (0.1–0.3%) and the median age of diagnosis is tend to be younger compared with that of PMBC and IMPC [14–16]. In this study, 40 cases of MMPC accounted for 0.21% (40/840 cases) of invasive breast cancer during the same period. The age of MMPC diagnosis was 30–80 years old, and the median age of onset was 57 years old. The above data were in accordance with the previous literatures.

In terms of histological morphology, the arrangement of MMPC is similar to that of IMPC. The arrangement of tumor cells of MMPC is pseudopapillary or pseudoglandular and EMA positive staining could be observed on the cell surface facing the surrounding extracellular mucin and the nuclear grade is mostly medium-high grade. The major difference between MMPC and IMPC is that MMPC tumor cells

float in a large amount of mucus while the key discrepancy between MMPC and PMBC is that PMBC lacks micropapillary structures [17, 18].

Several studies reported that MC mainly express MUC family of glycoproteins, for example MUC2, a gel-forming protein and is considered to be a barrier to tumor dissemination and makes MC indolent [19, 20]. This study demonstrated that the cases of positive staining of IPMC, MMPC and PMBC were 6 cases, 23 cases and 63, which implying that the positive expression of MUC2 in MMPC was similar to that of in PMBC. Eswari et al. also described a case of MC of the breast with neuroendocrine differentiation characteristic [21]. Tanuja et al. reported that 40.9% of MMPC cases expressed Syn and CgA [22]. In this research, we found that the number of positive expression of Syn in IPMC, MMPC and PMBC was 25 cases, 16 cases and 18 cases, which suggesting that the expression of neuroendocrine markers in MMPC was similar to that of IMPC.

As for molecular classification, previous study found that most PMBC belongs to Luminal A type while most IMPC belongs to Luminal B type [23]. However, the researches concerning the immunophenotyping and molecular classification of MMPC were rare. Barbashina et al. believed that the immunophenotype of MMPC is similar to that of PMBC, most of which are Luminal A type [15]. In addition, Mercogliano et al. reported positive HER2 overexpression in MMPC [17]. In this study, the molecular classification of 40 MMPC are as follows: Luminal A type 24 cases, Luminal B type 10 cases, HER2 overexpression type 3 cases, and basal-like type 3 cases. These data were in line with results of previous researches and MMPC shows unique features intermediate between those of PMBC and IMPC.

MMPC is relatively rare in clinical field, and the majority studies often focus on analyzing the pathological attribute while fail to explore the prognostic factors. Only Tanuja et al. reported that several elements may affect OS and DFS of MMPC, including histological type, nodal metastases, irregular tumor border, and IMPC type of local recurrence or metastases [22]. In this study, we also screened a number of potential prognostic factors, including tumor diameter, TNM stage, vascular invasion, lymph node metastasis, molecular classifications, status of Syn and Ki-67. Moreover, TNM stage and lymph node metastasis were two independent prognostic factors of MMPC.

There is one interesting issue we need to mention. Normally, triple-negative breast cancer (TNBC) exhibited more aggressive behavior, more frequent recurrence, and worse survival outcome compared with non-TNBC [24]. However, we witnessed different data in this present cohort study, from which TNBC cases did not encounter worst prognosis compared with non-TNBC cases. In my opinion, these inconsistency may be largely due to the small samples of TNBC. Future researches that enroll larger TNBC samples are of great importance.

To sum up, as a potential invasive BC with exclusive behaviors, deeply exploring the morphology and biological heterogeneity of MMPC is extremely critical. In this retrospective study, we enrolled MMPC, PMBC and IMPC samples simultaneously, compared their clinicopathological characteristics and identified several possible prognostic factors of MMPC. Our current findings widened the understanding

and categorized MMPC more accurately and may propose better individualized therapeutic strategies for MMPC treatment.

Conclusions

MMPC is a distinct subtype of breast cancer, which illustrated a number of particular characteristics, including prognostic properties. Further understanding and classification of MMPC may provide better individualized therapeutic strategies for MMPC treatment.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Human Research Ethics Committee of the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University ([2019]KY083-01).

Consent for publication

Written informed consents were obtained from the patients or family of the patient for publication of this cohort study.

Competing interests

All authors declare that they have no competing financial interests.

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Authors' contributions

XLZ designed the study. YYS, WXG, and GFW collected the tissue samples and clinical data. YYS and WXG performed the IHC analysis. YYS and GFW performed the statistics. YYS drafted the manuscript. XLZ supervised the study. All authors read and approved the final manuscript.

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Figures

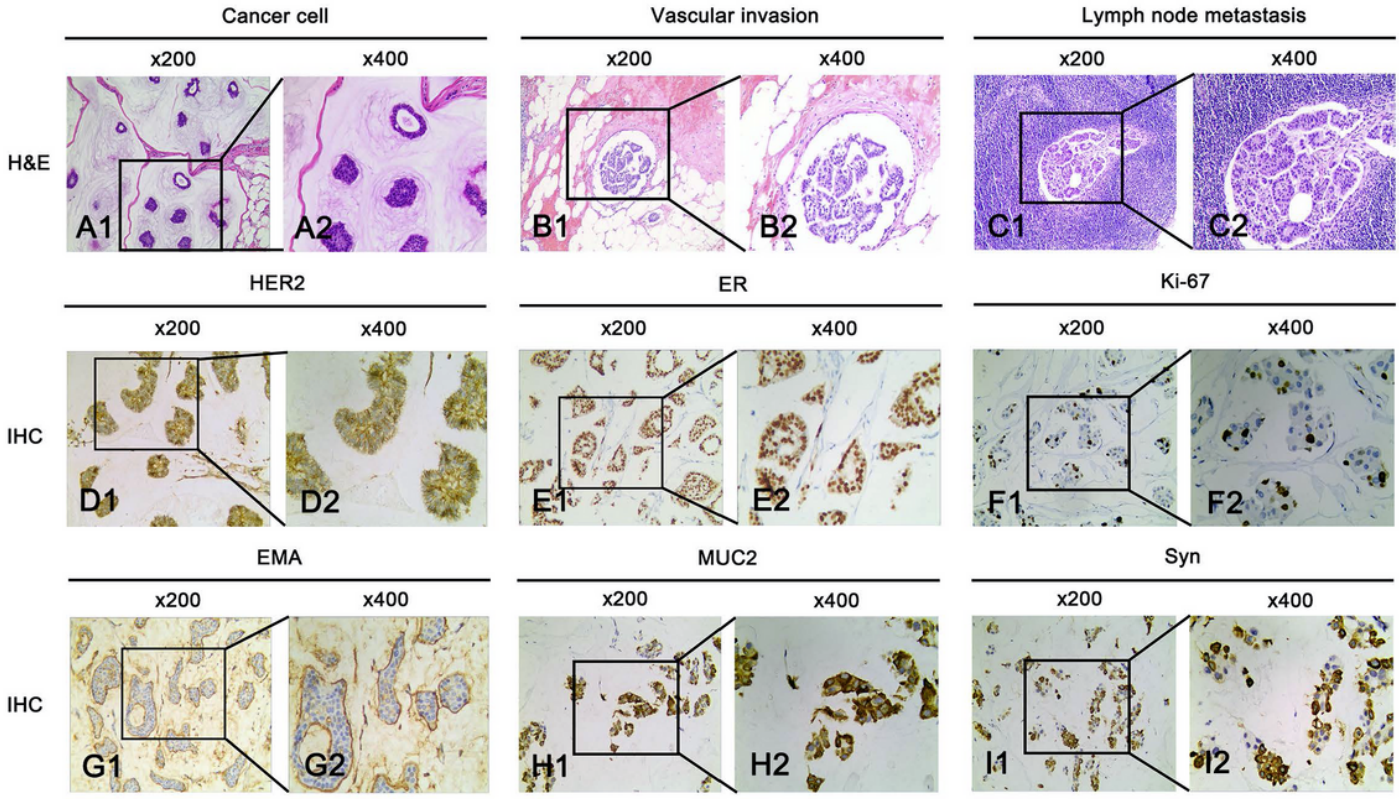

Figure 1

Representative H&E staining (A-C) and markers IHC staining (D-I) of MMPC samples. A1 and A2: cancer cell of MMPC. B1 and B2: vascular invasion of MMPC. C1 and C2: lymph node metastasis of MMPC. D1 and D2: Positive staining of HER2 of MMPC. E1 and E2: Positive staining of ER of MMPC. F1 and F2: Positive staining of Ki-67 of MMPC. G1 and G2: Positive staining of EMA of MMPC. H1 and H2: Positive staining of MUC2 of MMPC. I1 and I2: Positive staining of Syn of MMPC. Original magnification: ×200 in A1, B1, C1, D1, E1, F1, G1, H1, I1; ×400 in A2, B2, C2, D2, E2, F2, G2, H2, I2.

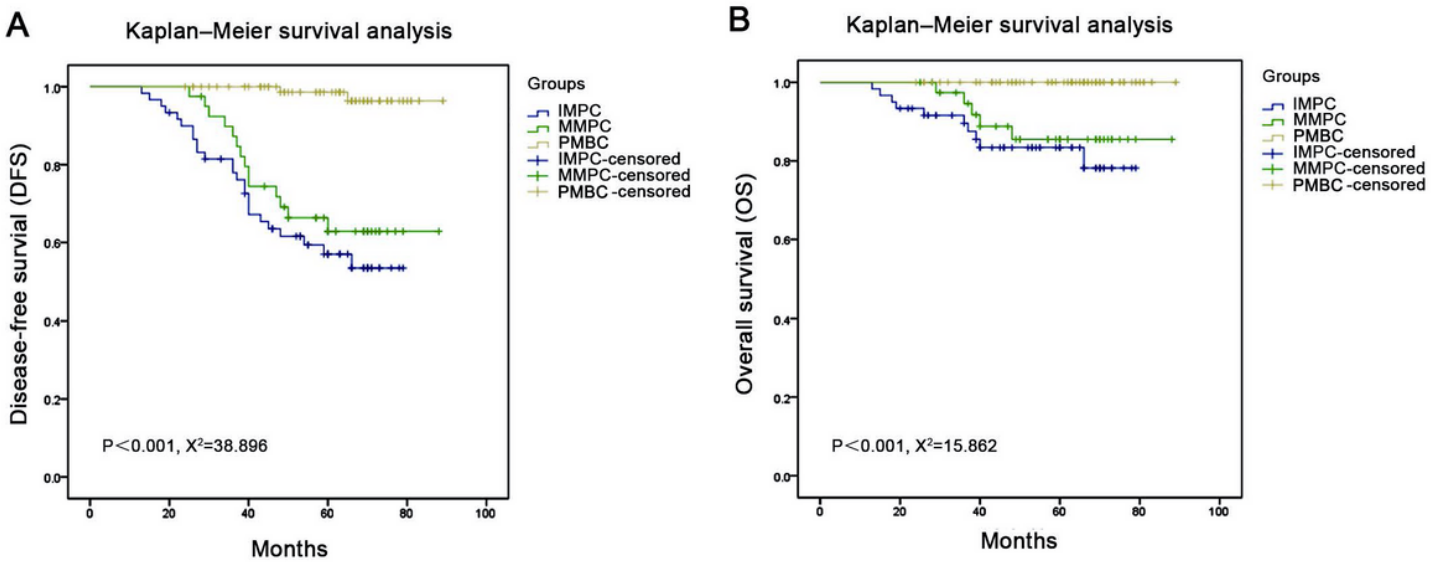

Figure 2

Survival analysis of MMPC, IMPC and PMBC patients by Kaplan-Meier method. A. Disease-free survival (DFS) in patients of MMPC (green line) was significantly lower than that in patients of PMBC (yellow line), while higher than that in patients of IMPC (blue line). B. Overall survival (OS) in patients of MMPC (green line) was significantly lower than that in patients of PMBC (yellow line), while higher than that in patients of IMPC (blue line).

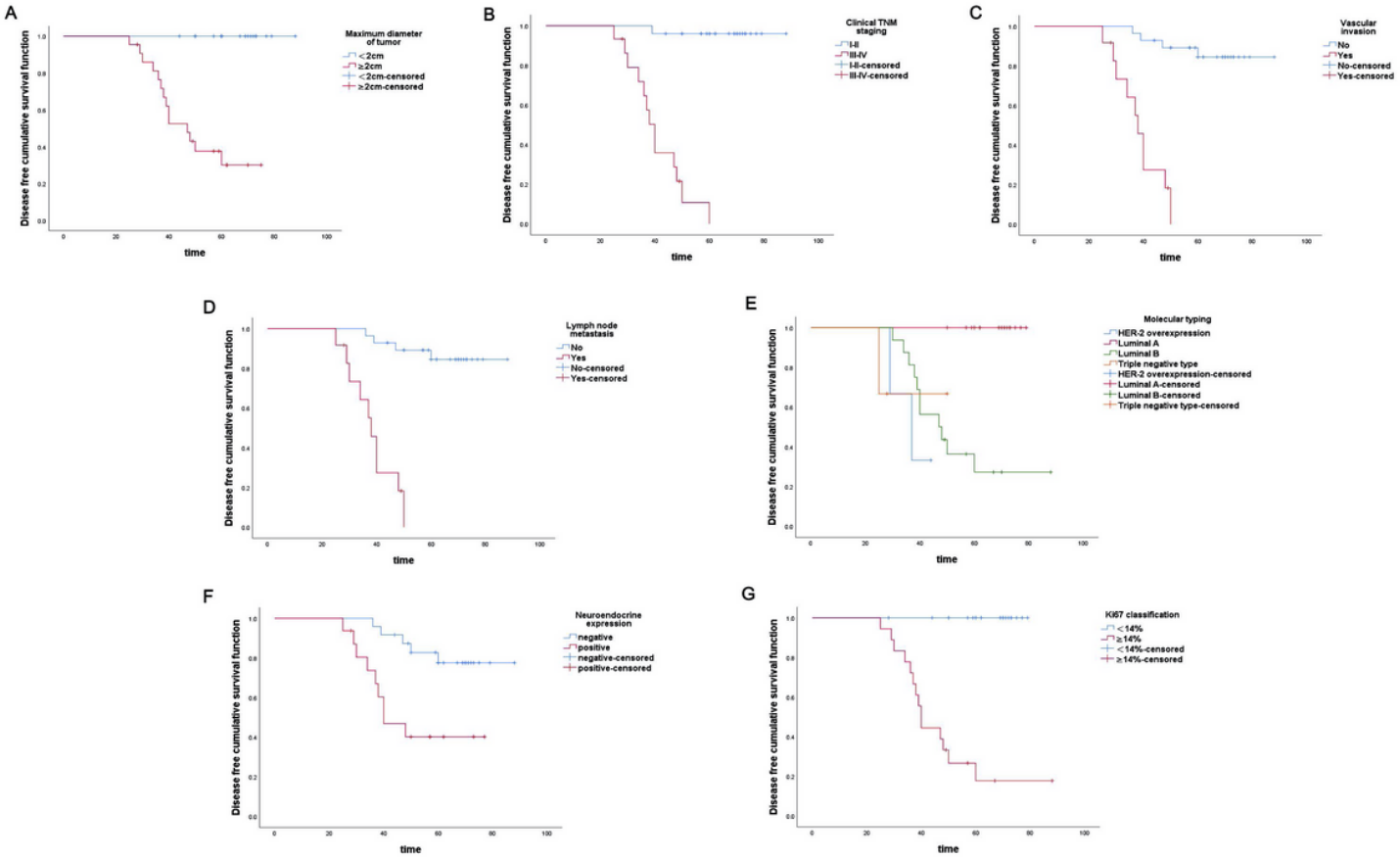

Figure 3

Survival analysis within MMPC. A. Disease-free survival (DFS) in patients with larger tumor diameter (≥2cm) (red line) was significantly lower than that in patients with smaller tumor diameter (<2cm) (blue line). B. DFS in patients with III-IV stage (red line) was significantly lower than that in patients with I-II stage (blue line). C. DFS in patients with positive vascular invasion (red line) was significantly lower than that in patients with negative vascular invasion (blue line). D. DFS in patients with positive lymph node metastasis (red line) was significantly lower than that in patients with negative lymph node metastasis (blue line). E. DFS in patients with Luminal B type (green line) was significantly lower than that in patients with Luminal A type (red line), HER2 overexpression type (blue line) and triple negative type (orange line). F. DFS in patients with positive neuroendocrine expression (red line) was significantly lower than that in patients with negative neuroendocrine expression (blue line). G. DFS in patients with high Ki-67

expression (red line) was significantly lower than that in patients with Ki-67 expression low Ki-67 expression (blue line).