Prognosis of subtypes of the mucinous breast carcinoma in Chinese women: a population-based study of 32-year experience (1983-2014)

Bo Pan¹,*, Ru Yao¹,*, Jie Shi²,*, Qian-Qian Xu¹, Yi-Dong Zhou¹, Feng Mao¹, Yan Lin¹, Jing-Hong Guan³, Xue-Jing Wang¹, Yan-Na Zhang¹, Xiao-Hui Zhang¹, Song-Jie Shen¹, Ying Zhong¹, Ya-Li Xu¹, Qing-Li Zhu³, Zhi-Yong Liang² and Qiang Sun¹

¹ Department of Breast Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, P. R. China
² Department of Pathology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, P. R. China
³ Department of Ultrasound, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, P. R. China

* These authors have contributed equally to this work

Correspondence to: Qiang Sun, email: sunqiangpumc@sina.com

Keywords: mucinous breast cancer, subtype, prognosis

Received: February 21, 2016 Accepted: April 04, 2016 Published: April 18, 2016

ABSTRACT

Purpose: The heterogeneous nature of the mucinous breast cancer (MBC), with its pure (PMBC) and mixed subtypes (MMBC), calls for precise prognosis assessment.

Methods: We analyzed 197 consecutive MBC patients, including 117 PMBC and 80 MMBC, who were treated from 1983 to 2014. The clinicopathological features, treatment choice, disease-free survival (DFS) and overall survival (OS) were compared among PMBC, MMBC and MMBC subgroups. Prognostic factors of PMBC and MMBC were identified.

Results: Compared to PMBC, MMBC had more lymph node metastasis (p = 0.043), Her2 positivity (p = 0.036), high Ki-67 index (defined as >20%, p = 0.026) and anti-Her2 targeted therapy (p = 0.016). The 5-year DFS of PMBC and MMBC were 90.4% and 86.2%, whereas the 5-year OS were 99.0% and 98.7%. No significant difference was found in DFS or OS among all MBC subtypes. High Ki-67 (p = 0.020) appeared as DFS factor in PMBC, while anti-Her2 targeted therapy (p = 0.047) as the DFS predictors in MMBC.

Conclusion: MMBC manifested similar 5-year survival to PMBC in Chinese woman, suggesting that intra-tumoral heterogeneity might not interfere with MBC short-term prognosis.

INTRODUCTION

Synonymous with colloid, gelatinous mucous or mucoid carcinoma, mucinous breast cancer (MBC) represents 1-7% of all breast cancers [1-5]. The World Health Organization designates two subtypes: 1) pure mucinous breast cancer (PMBC) if the non-mucinous component is less than 10% and 2) mixed mucinous breast cancer (MMBC) if there is 10-49% non-mucinous co-existing disease in the tumor [6, 7]. It is generally accepted that PMBC has a favorable prognosis in both Caucasian and Chinese women compared to invasive ductal carcinomas (IDC) [1, 2]. However, most of the studies proposing that MMBC had worse prognosis than PMBC were performed 2-3 decades ago, when modern adjuvant chemotherapy, radiation, endocrine and anti-Her2
targeted therapy were largely unavailable [3, 4, 8-10]. Few studies had investigated the tumor biology, treatment choice and survival outcomes of MMBC in Chinese population, especially with respect to the intra- and inter-tumoral histological heterogeneity represented by the different co-existing cancer components. The prognostic predictors for PMBC and MMBC also remained unclear. A recent study showed that both the mucinous and the co-existing components in MMBC were remarkably similar at the molecular level to PMBC, suggesting that MMBC be best classified as variants of mucinous cancers rather than of IDC [11]. Conversely PMBC appeared to possess phenotypic plasticity that could be converted by estrogen into MMBC with invasive lobular carcinoma (ILC) component [12]. Thus, we plan to compare the prognosis of PMBC versus MMBC in Chinese population when all measures of the modern comprehensive therapy were available.

RESULTS

Descriptive information of the study cohort

A total of 244 patients were identified as described in METHOD. After excluding 28 patients with < 50% focal mucinous lesion and 19 patients lost to follow-up, 197 patients were included in the analysis, comprising 1.9% of contemporary 10,192 breast cancer treated in PUMC Hospital. 171 patients (86.8%) were treated during the recent ten years (2005-2014) while 130 patients (66.0%) were treated during the recent five years (2010-2014). 112 patients (56.9%) were pre-menopausal and 85 (43.1%) post-menopausal. There were 117 PMBC and 80 MMBC patients, the latter including 24 patients with ductal carcinoma in situ (DCIS) and IDC (with or without other types of carcinoma), 45 with only IDC, 9 with invasive micro-papillary carcinoma (IMPC) and 2 with ILC. With a median follow-up time of 41 months (3-385 months), 11 PMBC and 7 MMBC patients developed recurrence or metastasis, and 1 PMBC and 1 MMBC passed away (Figure 1).

Comparison of clinicopathological characteristics between subtypes and subgroups of MBC

Compared to PMBC, MMBC had significantly more lymph node metastasis \( (p = 0.043) \), Her2 positivity \( (p = 0.036) \), high Ki-67 index \( (\text{defined as } > 20\%, p = 0.026) \) and anti-Her2 targeted therapy \( (p = 0.016) \). There were no significant differences in age at diagnosis, age group distribution, tumor size, TNM stage, ER, PR, hormone receptor status, immunophenotype, p53, type of surgery, chemotherapy, radiotherapy and endocrine therapy (Table 1). When the comparison was performed among PMBC, MBC+DCIS+IDC, MBC+IDC and MBC+IMPC, significant differences were identified in lymph node metastasis \( (p = 0.023) \), Her2 positivity \( (p = 0.014) \), high Ki-67 index \( (p = 0.008) \), chemotherapy \( (p = 0.011) \) and anti-Her2 targeted therapy \( (p = 0.002) \) (Table 2).

Survival outcomes and prognostic factors of MBC subtypes

The 5-year DFS of PMBC and MMBC were 90.4% and 86.2%, whereas the 5-year OS were 99.0% and 98.7% respectively. The 5-year DFS and OS for MMBC subgroups were: 85.7% and 100.0% for MBC+DCIS+IDC, 83.5% and 97.6% for MBC+IDC, and 100.0% and 100.0% for MBC+IMPC. No significant difference was found in DFS or OS either between PMBC vs MMBC or among the above mentioned MMBC subgroups (Figure 2, Table 3, 4). High Ki-67 index \( (\text{defined as } > 20\%, p = 0.020) \) was identified as the significant DFS prognostic factor for PMBC, whereas anti-Her2 targeted therapy \( (p = 0.047) \) appeared to be the DFS predictor for MMBC (Table 5, 6). DFS stratified by Ki-67 in PMBC and by anti-Her2 targeted therapy in MMBC both showed significant differences (Figure 2). ER, PR, hormone receptor status, immunophenotype and endocrine therapy might be potential DFS predictors according to univariate analysis. However, these factors were not significant in the multivariate analysis. None of the clinicopathological and treatment factors listed above could serve as OS predictors for MBC subtypes due to the limited OS events.

DISCUSSION

MBC is one of the most commonly seen special types of breast cancer [1, 2, 4, 8]. Experience in diagnosis and treatment of MBC was usually acquired from retrospective studies instead of prospective randomized trials. It was widely believed that MMBC had a poorer prognosis than PMBC [3, 4, 8-10]. However, these retrospective studies were mainly based on data from Caucasian, and mostly performed during the 1960s to 1980s, when anti-Her2 targeted therapy, most of the endocrine therapy, chemotherapy and radiation therapy were unavailable. Thus the poorer outcome of MMBC might be due to insufficient treatment. Additionally, MMBC is not a single disease. Whether MMBC subgroups have different survival outcomes remains unclear. A recent study reported differences in breast cancer epidemiology, clinical characteristics and prognosis between Chinese and Caucasian women [13, 14]. However, few studies have evaluated the survival outcome among MBC subtypes in Chinese women, who tend to develop breast cancer and MBC at a much younger age than Caucasian counterparts [1, 2, 5, 15, 16].

Although PMBC usually had normal diploid DNA
| Characteristics                  | No. (%) of Patients | PMBC   | MMBC   | P<sup>a</sup> |
|---------------------------------|---------------------|--------|--------|---------------|
| **Total**                       |                     | 117    | 80     |               |
| Age (Mean±SD) (years)           |                     | 53.26±15.25 | 55.90±14.38 | 0.223         |
| Age at diagnosis (years)        |                     |        |        | 0.432         |
| ≤35                             | 10 (8.5)            | 5 (6.2)  |        |               |
| 36~50                           | 52 (44.5)           | 30 (37.5) |        |               |
| >50                             | 55 (47.0)           | 45 (56.3) |        |               |
| Tumor size (cm)                 |                     |        |        | 0.480         |
| T≤2.0                           | 59 (50.4)           | 43 (53.8) |        |               |
| 2<T≤5.0                         | 49 (41.9)           | 31 (38.8) |        |               |
| T>5.0                           | 4 (3.4)             | 5 (6.2)  |        |               |
| Unknown                         | 5 (4.3)             | 1 (1.2)  |        |               |
| **Lymph node status**           |                     |        |        | 0.043         |
| Negative                        | 103 (88.0)          | 64 (80.0) |        |               |
| Positive                        | 11 (9.4)            | 16 (20.0) |        |               |
| Unknown                         | 3 (2.6)             | 0 (0.0)  |        |               |
| **TNM stage**<sup>b</sup>       |                     |        |        | 0.147         |
| Stage I                         | 55 (47.0)           | 35 (43.8) |        |               |
| Stage II                        | 53 (45.3)           | 35 (43.8) |        |               |
| Stage III                       | 6 (5.1)             | 10 (12.5) |        |               |
| Unknown                         | 3 (2.6)             | 0 (0.0)  |        |               |
| **ER status**                   |                     |        |        | 0.484         |
| Positive                        | 94 (80.3)           | 66 (82.5) |        |               |
| Negative                        | 12 (10.3)           | 10 (12.5) |        |               |
| Unknown                         | 11 (9.4)            | 4 (5.0)  |        |               |
| **PR status**                   |                     |        |        | 0.834         |
| Positive                        | 88 (75.3)           | 62 (77.6) |        |               |
| Negative                        | 19 (16.2)           | 13 (16.2) |        |               |
| Unknown                         | 10 (8.5)            | 5 (6.2)  |        |               |
| **Hormone receptor status**     |                     |        |        | 0.631         |
| Positive                        | 98 (83.8)           | 70 (87.5) |        |               |
| Negative                        | 9 (7.7)             | 6 (7.5)  |        |               |
| Unknown                         | 10 (8.5)            | 4 (5.0)  |        |               |
| HER2 status        |       |       |
|--------------------|-------|-------|
| Positive           | 3 (2.6) | 9 (11.2) |
| Negative           | 97 (82.9) | 58 (72.5) |
| Unknown            | 17 (14.5) | 13 (16.2) |

| Ki-67 expression   |       |       |
|--------------------|-------|-------|
| <20%               | 64 (54.7) | 36 (45.0) |
| ≥20%               | 29 (24.8) | 34 (42.5) |
| Unknown            | 24 (20.5) | 10 (12.5) |

| Immunophenotype    |       |       |
|--------------------|-------|-------|
| Luminal A          | 62 (53.0) | 32 (40.0) |
| Luminal B          | 29 (24.8) | 32 (40.0) |
| HER2               | 0 (0.0) | 1 (1.2) |
| TNBC               | 8 (6.8) | 5 (6.2) |
| Unknown            | 18 (15.4) | 10 (12.5) |

| p53                |       |       |
|--------------------|-------|-------|
| Positive           | 6 (5.1) | 6 (7.5) |
| Negative           | 46 (39.3) | 26 (32.5) |
| Unknown            | 65 (55.6) | 48 (60.0) |

| Surgery            |       |       |
|--------------------|-------|-------|
| Mastectomy         | 75 (64.1) | 52 (65.0) |
| Breast conserving  | 42 (35.9) | 28 (35.0) |
| Unknown            | 0 (0.0) | 0 (0.0) |

| Chemotherapy       |       |       |
|--------------------|-------|-------|
| No                 | 69 (59.0) | 41 (51.2) |
| Yes                | 43 (36.8) | 38 (47.5) |
| Unknown            | 5 (4.2) | 1 (1.2) |

| Radiotherapy       |       |       |
|--------------------|-------|-------|
| No                 | 82 (70.1) | 57 (71.3) |
| Yes                | 26 (22.2) | 21 (20.2) |
| Unknown            | 9 (7.7) | 2 (2.5) |

| Anti-Her2 targeted therapy |       |       |
|---------------------------|-------|-------|
| No                        | 107 (91.5) | 70 (87.5) |
| Yes                       | 2 (1.7) | 8 (10.0) |
stemline whereas MMBC harbored aneuploid DNA content, a recent study suggested that MBC subtypes based on gene expression profiling might be more complex than anticipated [17, 18]. Unsupervised clustering analysis showed that MMBC displayed similar patterns of genetic aberrations and preferentially clustered together with...
Figure 2: Kaplan-Meier estimates of DFS and OS of MBC patients. DFS A. and OS B. compared between PMBC and MMBC patients. The comparison of DFS C. and OS D. of PMBC, MBC+DCIS+IDC, MBC+IDC, and MBC+IMPC patients. DFS of PMBC patients compared between subgroups of Ki-67 high (defined as ≥ 20%) versus Ki-67 low (defined as < 20%) E. DFS of MMBC patients compared between patient subgroups with or without anti-Her2 targeted therapy F.
Table 2: Comparison of the clinicopathological characteristics of PMbc versus subgroups of MMbc including MBC+DCIS+IDC, MBC+IDC and MBC+IMPC patients

| Characteristics                      | No. (%) of Patients |  |  |  |
|--------------------------------------|---------------------|-----------------|-----------------|-----------------|-----------------|
|                                      | PMBC                | MBC+DCIS+IDC    | MBC+IDC         | MBC+IMPC        |
| Total                                | 117 (100.0)         | 24 (100.0)      | 45 (100.0)      | 9 (100.0)       |
| Age (Mean±SD) (years)                | 53.3±15.3           | 56.6±12.6       | 54.7±15.2       | 61.8±15.4       | 0.333           |
| Age at diagnosis (years)             |                     |                 |                 |                 | 0.612           |
| ≤35                                  | 10 (8.5)            | 0 (0.0)         | 4 (8.9)         | 1 (11.1)        |
| 36~50                                | 52 (44.5)           | 10 (41.7)       | 17 (37.8)       | 2 (22.2)        |
| >50                                  | 55 (47.0)           | 14 (58.3)       | 24 (53.3)       | 6 (66.7)        |
| Tumor size (cm)                      |                     |                 |                 |                 | 0.204           |
| T≤2.0                                | 59 (50.4)           | 18 (75.0)       | 19 (42.2)       | 5 (56.6)        |
| 2<T≤5.0                              | 49 (41.9)           | 4 (16.7)        | 24 (53.3)       | 3 (33.3)        |
| >5.0                                 | 4 (3.4)             | 1 (4.2)         | 2 (4.4)         | 1 (11.1)        |
| Lymph node status                    |                     |                 |                 |                 | 0.023           |
| Negative                             | 103 (88.0)          | 22 (91.7)       | 32 (71.1)       | 9 (100.0)       |
| Positive                             | 11 (9.4)            | 2 (8.3)         | 13 (28.9)       | 0 (0.0)         |
| Unknown                              | 3 (2.6)             | 0 (0.0)         | 0 (0.0)         | 0 (0.0)         |
| TNM stagea                           | 0.069               |                 |                 |                 |                 |
| Stage I                              | 55 (47.0)           | 16 (66.7)       | 13 (28.9)       | 5 (55.6)        |
| Stage II                             | 53 (45.3)           | 6 (25.0)        | 25 (55.6)       | 4 (44.4)        |
| Stage III                            | 6 (5.1)             | 2 (8.3)         | 7 (15.6)        | 0 (0.0)         |
| Unknown                              | 3 (2.6)             | 0 (0.0)         | 0 (0.0)         | 0 (0.0)         |
| ER status                            | 0.587               |                 |                 |                 |                 |
| Positive                             | 94 (80.3)           | 22 (91.7)       | 34 (75.6)       | 8 (88.9)        |
| Negative                             | 12 (10.3)           | 2 (8.3)         | 7 (15.6)        | 1 (11.1)        |
| Unknown                              | 11 (9.4)            | 0 (0.0)         | 4 (8.9)         | 0 (0.0)         |
| PR status                            | 0.816               |                 |                 |                 |                 |
| Positive                             | 88 (75.2)           | 21 (87.5)       | 33 (73.3)       | 7 (77.8)        |
| Negative                             | 19 (16.2)           | 2 (8.3)         | 8 (17.8)        | 2 (22.2)        |
| Unknown                              | 10 (8.5)            | 1 (4.2)         | 4 (8.9)         | 0 (0.0)         |
| Hormone receptor status              | 0.694               |                 |                 |                 |                 |
| Positive                             | 98 (83.8)           | 23 (95.8)       | 37 (82.2)       | 8 (88.9)        |
| Negative                             | 9 (7.7)             | 1 (4.2)         | 4 (8.9)         | 1 (11.1)        |
| Unknown                              | 10 (8.5)            | 0 (0.0)         | 4 (8.9)         | 0 (0.0)         |
| HER2 status                          | 0.014               |                 |                 |                 |                 |
| Positive                             | 98 (83.8)           | 23 (95.8)       | 37 (82.2)       | 8 (88.9)        |
| Negative                             | 9 (7.7)             | 1 (4.2)         | 4 (8.9)         | 1 (11.1)        |
| Unknown                              | 10 (8.5)            | 0 (0.0)         | 4 (8.9)         | 0 (0.0)         |
| Positive | 3 (2.6) | 1 (4.2) | 8 (17.8) | 0 (0.0) |
|----------|---------|---------|----------|---------|
| Negative | 97 (82.9) | 20 (83.3) | 28 (62.2) | 8 (88.9) |
| Unknown  | 17 (14.5) | 3 (12.5) | 9 (20.0) | 1 (11.1) |

**Ki-67 expression**  
0.008

| <20% | 64 (54.7) | 16 (66.7) | 14 (31.1) | 6 (66.7) |
| ≥20% | 29 (24.8) | 5 (20.8) | 24 (53.3) | 3 (33.3) |
| Unknown | 24 (20.5) | 3 (12.5) | 7 (15.6) | 0 (0.0) |

**Immunophenotype**  
0.105

| Luminal A | 62 (53.0) | 15 (62.5) | 12 (26.7) | 5 (55.6) |
| Luminal B | 29 (24.8) | 5 (20.8) | 22 (48.9) | 3 (33.3) |
| HER2 | 0 (0.0) | 0 (0.0) | 1 (2.2) | 0 (0.0) |
| TNBC | 8 (6.8) | 1 (4.2) | 3 (6.7) | 1 (11.1) |
| Unknown | 18 (15.4) | 3 (12.5) | 7 (15.6) | 0 (0.0) |

**p53**  
0.418

| Positive | 6 (5.1) | 0 (0.0) | 5 (11.1) | 1 (11.1) |
| Negative | 46 (39.3) | 7 (29.2) | 16 (35.6) | 2 (22.2) |
| Unknown | 65 (55.6) | 17 (70.8) | 24 (53.3) | 6 (66.7) |

**Surgery**  
0.575

| Mastectomy | 75 (64.1) | 15 (62.5) | 31 (68.9) | 4 (44.4) |
| Breast conserving | 42 (35.9) | 9 (37.5) | 14 (31.1) | 5 (55.6) |
| Unknown | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

**Chemotherapy**  
0.011

| No | 69 (59.0) | 18 (75.0) | 16 (35.6) | 6 (66.7) |
| Yes | 43 (36.8) | 5 (20.8) | 29 (64.4) | 3 (33.3) |
| Unknown | 5 (4.2) | 1 (4.2) | 0 (0.0) | 0 (0.0) |

**Radiotherapy**  
0.299

| No | 82 (70.1) | 19 (79.2) | 30 (66.7) | 6 (66.7) |
| Yes | 26 (22.2) | 4 (16.7) | 15 (33.3) | 3 (33.3) |
| Unknown | 9 (7.7) | 1 (4.1) | 0 (0.0) | 0 (0.0) |

**Anti-Her2 targeted therapy**  
0.002

| No | 107 (91.5) | 23 (95.8) | 36 (80.0) | 9 (100.0) |
| Yes | 2 (1.7) | 0 (0.0) | 8 (17.8) | 0 (0.0) |
| Unknown | 8 (6.8) | 1 (4.1) | 1 (2.2) | 0 (0.0) |

**Endocrine therapy**  
0.566

| No | 15 (12.8) | 1 (4.2) | 6 (13.3) | 1 (11.1) |
| Yes | 91 (77.8) | 21 (87.5) | 38 (84.4) | 8 (88.9) |
| Unknown | 11 (9.4) | 2 (8.3) | 1 (2.2) | 0 (0.0) |

Abbreviations: PMBC, pure mucinous breast cancer; MBC, mucinous breast cancer; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; IMPC, invasive micropapillary carcinoma; SD, standard deviation; TNM, tumor, node, metastasis system; ER, estrogen receptor; PR, progesterone receptor.

- Bold type indicates statistical significance.
- TNM stage is according to the 7th AJCC cancer staging system.
PMBC rather than with IDC [11]. A study with MBC cell line and xenograft model also showed that PMBC manifested phenotypic plasticity and could be converted by estrogen into MMBC with ILC [12]. This genotypic and phenotypic similarity between PMBC and MMBC provides explanation for their similar prognosis. Secretory mucins (MUC2 and MUC6) and the mucus might also act as a barrier to cancerous extension and decrease the aggressiveness of the tumor biology [8, 19].

In our study, the difference in lymph node (LN) metastasis between PMBC, MMBC and MMBC subtypes might be due to distinct tumor biology. However, the MBC were diagnosed at similar T stage and hence have no significant differences in pTNM stage. Our result on MBC survival coincided with the study from Park S et al. reporting similar 10-year DFS and OS between PMBC and MMBC [20]. Bae SY et al. reported similar DFS and different OS ($p = 0.043$), however, their study did not

| Group          | No. of patients | 5-year DFS (%) | P    | 5-year OS (%) | P    |
|----------------|----------------|----------------|------|---------------|------|
| PMBC           | 117            | 90.4           | 0.405| 99.0          | 0.765|
| MMBC           | 80             | 86.2           |      | 98.7          |      |

Abbreviations: PMBC, pure mucinous breast cancer; MMBC, mixed mucinous breast cancer; DFS, disease free survival; OS, overall survival.

| Group                      | No. of patients | 5-year DFS (%) | P    | 5-year OS (%) | P    |
|----------------------------|-----------------|----------------|------|---------------|------|
| PMBC                       | 117             | 90.4           |      | 99.0          |      |
| MBC+DCIS+IDC              | 24              | 85.7           | 0.240| 100.0         | 0.784|
| MBC+IDC                   | 45              | 83.5           |      | 97.6          |      |
| MBC+IMPC                  | 9               | 100.0          |      | 100.0         |      |

Abbreviations: MBC, mucinous breast cancer; PMBC, pure mucinous breast cancer; MMBC, mixed mucinous breast cancer; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; IMPC, invasive micropapillary carcinoma; DFS, disease free survival; OS, overall survival.

| Variables           | Univariatea | Multivariateb |
|---------------------|-------------|---------------|
| Age at diagnosis    | 0.170       | 0.082         |
| Tumor size          | 0.415       | 0.466         |
| Lymph node status   | 0.331       | 0.218         |
| TNM staged          | 0.831       | 0.593         |
| ER status           | 0.697       | 0.963         |
| PR status           | 0.496       | 0.210         |
| Hormone receptor status | 0.741    | 0.973         |
| HER2 status         | 0.631       | 0.476         |
| Ki-67 expression    | 0.046       | **0.020**     |
| Immunophenotype     | 0.111       | 0.067         |
| p53                 | 0.801       | 0.230         |
| Surgery             | 0.054       | 0.070         |
| Chemotherapy        | 0.379       | 0.082         |
| Radiotherapy        | 0.738       | 0.070         |
| Anti-Her2 targeted therapy | 0.874 | 0.466         |
| Endocrine therapy   | 0.945       | 0.218         |

| Variables           | Univariatea | Multivariateb |
|---------------------|-------------|---------------|
| Age at diagnosis    | 0.170       | 0.082         |
| Tumor size          | 0.415       | 0.466         |
| Lymph node status   | 0.331       | 0.218         |
| TNM staged          | 0.831       | 0.593         |
| ER status           | 0.697       | 0.963         |
| PR status           | 0.496       | 0.210         |
| Hormone receptor status | 0.741    | 0.973         |
| HER2 status         | 0.631       | 0.476         |
| Ki-67 expression    | 0.046       | **0.020**     |
| Immunophenotype     | 0.111       | 0.067         |
| p53                 | 0.801       | 0.230         |
| Surgery             | 0.054       | 0.070         |
| Chemotherapy        | 0.379       | 0.082         |
| Radiotherapy        | 0.738       | 0.070         |
| Anti-Her2 targeted therapy | 0.874 | 0.466         |
| Endocrine therapy   | 0.945       | 0.218         |

Abbreviations: PMBC, pure mucinous breast cancer; ER, estrogen receptor; PR, progesterone receptor.

a Kaplan-Meier univariate analysis including all factors.
b Adjusted by Cox proportional hazard regression model including all factors with method of enter.
c Bold type indicates statistical significance.
d TNM stage is according to the 7th AJCC cancer staging system.

| Table 3: Kaplan-Meier estimated DFS and OS rates compared between PMBC and MMBC |
|-------------------------------------|----------------|----------------|--------|
| Group                              | No. of patients | 5-year DFS (%) | P      | 5-year OS (%) | P      |
| PMBC                               | 117             | 90.4           | 0.405  | 99.0          | 0.765  |
| MMBC                               | 80              | 86.2           |        | 98.7          |        |

Abbreviations: PMBC, pure mucinous breast cancer; MMBC, mixed mucinous breast cancer; DFS, disease free survival; OS, overall survival.

| Table 4: Kaplan-Meier estimated DFS and OS rates compared between PMBC, MBC+DCIS+IDC, MBC+IDC and MBC+IMPC |
|------------------------------------------------------|----------------|----------------|--------|
| Group                                               | No. of patients | 5-year DFS (%) | P      | 5-year OS (%) | P      |
| PMBC                                                 | 117             | 90.4           | 0.240  | 99.0          | 0.784  |
| MBC+DCIS+IDC                                        | 24              | 85.7           |        | 100.0         |        |
| MBC+IDC                                              | 45              | 83.5           |        | 97.6          |        |
| MBC+IMPC                                             | 9               | 100.0          |        | 100.0         |        |

Abbreviations: MBC, mucinous breast cancer; PMBC, pure mucinous breast cancer; MMBC, mixed mucinous breast cancer; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; IMPC, invasive micropapillary carcinoma; DFS, disease free survival; OS, overall survival.

| Table 5: Univariate and multivariate Cox analysis of disease-free survival of patients with PMBC |
|---------------------------------------------------|-------------|----------------|--------|
| Variables                                         | Univariatea | Multivariateb |
| Age at diagnosis                                   | 0.170       | 0.082         |
| Tumor size                                        | 0.415       | 0.466         |
| Lymph node status                                 | 0.331       | 0.218         |
| TNM staged                                        | 0.831       | 0.593         |
| ER status                                         | 0.697       | 0.963         |
| PR status                                         | 0.496       | 0.210         |
| Hormone receptor status                           | 0.741       | 0.973         |
| HER2 status                                       | 0.631       | 0.476         |
| Ki-67 expression                                   | 0.046       | **0.020**     |
| Immunophenotype                                   | 0.111       | 0.067         |
| p53                                               | 0.801       | 0.230         |
| Surgery                                           | 0.054       | 0.070         |
| Chemotherapy                                      | 0.379       | 0.082         |
| Radiotherapy                                      | 0.738       | 0.070         |
| Anti-Her2 targeted therapy                        | 0.874       | 0.466         |
| Endocrine therapy                                 | 0.945       | 0.218         |

Abbreviations: PMBC, pure mucinous breast cancer; ER, estrogen receptor; PR, progesterone receptor.

a Kaplan-Meier univariate analysis including all factors.
b Adjusted by Cox proportional hazard regression model including all factors with method of enter.
c Bold type indicates statistical significance.
d TNM stage is according to the 7th AJCC cancer staging system.
review pTNM stage, Ki-67, anti-Her2 targeted therapy [21]. Additionally, the age at diagnosis of MBC patients was much younger than contemporary IDC in Korean women, which was different from both Caucasian and Chinese [1, 2, 5, 20, 21]. Zhang M et al. reported better PMBC survival than MMBC in Chinese population [5]. However, most of the MMBC patients included in that study were diagnosed at a much later stage than PMBC, while 70.5% of PMBC patients received chemotherapy. There was no data concerning the Her2 status so that the similar percentage of anti-Her2 targeted therapy between MBC vs non-MBC or between PMBC vs MMBC would be difficult to interpret.

Compared with IDC, IMPC usually has larger size, more metastatic lymph nodes, increased lymphovascular invasion (LVI) and more aggressive behavior [22]. Poorer survival was also observed for breast carcinoma containing IMPC component [22]. Notably, a special subtype of PMBC with micropapillary epithelial growth pattern was identified as invasive micropapillary mucinous carcinoma (IMPMC) [23], or mucinous carcinomas with a micropapillary pattern (MUMPC) [24]. This heterogeneous PMBC had more LN metastasis, higher Her2 expression, LVI, and a poorer prognosis than pure PMBC [23, 24]. Meanwhile, it showed decreased LN metastasis, lower nuclear grade, higher expression of ER and PR, less expression of Her2, and better prognosis compared to IMPC. Though controversial, it was proposed that PMBC, MUMPC/IMPMC and IMPC might represent clinical entities within a spectrum of heterogeneous diseases, with different percentage of mucin secretion and micropapillary components [23-25]. The MBC+IMPC in our study was different from MUMPC/IMPMC and did not exhibit higher LN metastasis, higher Her2 or Ki-67 expression, or poorer survival outcome.

Our study had several limitations. Firstly, it was a single-center study with limited case number, and two patients with MBC+ILC had to be excluded from the comparison. Secondly, although this retrospective study reviewed MBC patients distributed during 32 years’ time span, majority (86.8%) of patients was treated in the recent decade (2005-2014), so it would make more sense to analyze the 5-year short-term survival. There might still be significant difference in long-term 10-year prognosis between PMBC and MMBC, because MBC is basically luminal subtype and have shown late recurrences after 10 years [24, 26]. Thirdly, LN metastasis was not identified as the DFS predictor in our study, although it was identified in other studies to be candidate prognostic factor for PMBC [1, 2, 8, 21, 26, 27]. Fourthly, Ki-67 expression was only documented in 79.5% of the PMBC and 87.5% of the MMBC, while p53 status in more than half of the cases was unknown.

In conclusion, our study revealed that MMBC had similar short-term survival as PMBC in Chinese patients, suggesting that intra-tumoral heterogeneity might not

| Variables                     | Univariate | Multivariate |
|-------------------------------|------------|--------------|
| Pathologic types              | 0.460      | 0.344 (0.015-8.149) | 0.509 |
| Age at diagnosis              | 0.606      | 1.083 (0.048-24.428) | 0.960 |
| Tumor size                    | 0.764      | 0.052 (0.000-31.232) | 0.364 |
| Lymph node status             | 0.573      | 0.000 (0.000-355.483) | 0.145 |
| TNM staged                    | 0.618      | 3154 (0.032-3126) | 0.170 |
| ER status                     | 0.000      | 0.004 (0.000-5.52) | 0.136 |
| PR status                     | 0.005      | 3.696 (0.039-347.957) | 0.573 |
| Hormone receptor status       | 0.000      | 3.246 (0.004-2777) | 0.733 |
| HER2 status                   | 0.504      | 0.092 (0.002-3.521) | 0.199 |
| Ki-67 expression              | 0.302      | 12.349 (0.005-33822) | 0.534 |
| Immunophenotype               | 0.000      | 1.055 (0.055-20.270) | 0.971 |
| p53                           | 0.067      | 2.025 (0.086-47.626) | 0.662 |
| Surgery                       | 0.962      | 0.025 (0.000-176.301) | 0.414 |
| Chemotherapy                  | 0.232      | 0.172 (0.001-23.738) | 0.483 |
| Radiotherapy                  | 0.473      | 27.030 (0.012-60963) | 0.403 |
| Anti-Her2 targeted therapy    | 0.000      | 6977 (1.1410-42696079) | 0.047 |
| Endocrine therapy             | 0.003      | 0.071 (0.001-3.380) | 0.180 |

Table 6: Univariate and multivariate Cox analysis of disease-free survival of patients with MMBC

Abbreviations: MMBC, mixed mucinous breast cancer; ER, estrogen receptor; PR, progesterone receptor.

a Kaplan-Meier univariate analysis including all factors.
b Adjusted by Cox proportional hazard regression model including all factors with method of enter.
c Bold type indicates statistical significance.
d TNM stage is according to the 7th AJCC cancer staging system.
interfere with MBC prognosis in Chinese women. Ki-67 proliferation index was identified as a DFS prognostic factor for PMBC, whereas anti-Her2 targeted therapy as the potential DFS predictor for MMBC. Further studies with increased cases number, prolonged follow-up and improved bio-markers need to be performed to gain a deeper understanding of MBC biology and prognosis with respect to intra- and inter-tumoral heterogeneity.

MATERIALS AND METHODS

Ethics statement

This study was approved by the Ethics Committee of the Peking Union Medical College Hospital, Chinese Academy of Medical Sciences.

Patient selection, pathology review and follow-up

From January 1983 to December 2014, 244 consecutive MBC patients were treated primarily with breast cancer surgeries in PUMC Hospital according to the medical records searching. All patients’ formalin-fixed paraffin-embedded (FFPE) pathological sections were reviewed and 28 patients with focal mucinous components < 50% of the total cancerous lesions were excluded from the study. All patients were followed by telephone call, by out-patient clinics records of follow-up examinations or by both measures. Another 19 patients who were lost to follow-up were also excluded.

There were 197 MBC patients, including 117 PMBC and 80 MMBC, in the study cohort. The clinicopathological characteristics, treatment choice, DFS and OS were compared both between 117 PMBC vs 80 MMBC, and among all MBC subgroups, including 24 MMBC with DCIS and IDC (with or without other types of carcinoma), 45 with only IDC and 9 with IMPC. Two patients with MMBC and ILC were excluded from the comparison due to the small case number. DFS factors of PMBC and MMBC were identified respectively. Identification of prognostic factors for MMBC subgroups were not performed also due to the limited case numbers (Figure 1).

Statistical analysis

The quantitative variables were compared with t-test and the categorical variables were compared with chi-square tests. Survival outcomes including 5-year predicted DFS and OS were analyzed and compared by the Kaplan-Meier curve method. Kaplan-Meier univariate analyses and Cox multivariate analyses were performed to identify the prognostic factors for PMBC and MMBC respectively. The significance threshold was set at $p < 0.05$. SPSS software, version 18.0 (SPSS, Inc. Chicago, IL, US) was used for all of the statistical analyses.

ACKNOWLEDGMENTS

We would like to thank all of the patients for their participation in this study.

FUNDING SUPPORT

This work was supported by the Twelfth Five Year Key Programs for Science and Technology Development of China (Grant No. 2014BAI028B03) and the Natural Science Foundation of China (Grant No. 81001183).

CONFLICTS OF INTEREST

The authors have declared that no competing interests exist.

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