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CLINICAL TRIAL

Prognosis in different subtypes of metaplastic breast cancer: a population-based analysis

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Abstract

Background Metaplastic breast cancer (MpBC) is a rare histological subtype of breast cancer recognized as a unique pathologic entity in 2000. However, the pathogenesis, optimal therapy, and prognosis of MpBC and the potential effect of systemic treatments on different subtypes of MpBC are not well defined.

Methods A retrospective population-based study was performed to identify breast cancer patients with MpBC and other triple-negative breast cancers (TNBC) between 2010 and 2014 using the surveillance, Epidemiology, and End Results (SEER) database. Chi-square test was used to analyze characteristics between subgroups. Kaplan–Meier analysis and Multivariate Cox regressions were used to evaluate overall survival (OS) of MpBC, TNBC, and MpBC subgroups. Competing risk analysis and multivariate regression model of competing risk were used to assess breast cancer-specific survival (BCSS) of MpBC and TNBC

Results We identified a study cohort of 22,433 patients (1112 MpBC and 21,321 TNBC). MpBC correlated with older population, larger tumor size and less lymph node involvement, and TNBC phenotype. Patients with MpBC especially with triple-negative subtype (TN-MpBC) had worse survival than the overall TNBC population. However, the prognosis of MpBC without triple-negative subtype (non-TN MpBC) was not different from that of TNBC. In Kaplan–Meier analysis, chemotherapy was not associated with significant difference in OS of TN-MpBC. In non-TN MpBC group, the 3-year OS was 79.8% for patients receiving chemotherapy and 70.5% in patients without chemotherapy, and chemotherapy was associated ($P=0.033$) with improved OS. Within the MpBC patients, radiotherapy was significantly (HR 1.544; 95% CI 1.148–2.078; $P=0.004$) associated with improved OS and (HR 1.474; 95% CI 1.067–2.040; $P=0.019$) BCSS.

Conclusions Patients with TN-MpBC had worse prognosis than TNBC and chemotherapy was not associated with improved survival. In contrast, non-TN MpBC may derive survival benefit from chemotherapy and radiotherapy.

Keywords Metaplastic breast cancer · Breast cancer subtype · Chemotherapy · Radiotherapy · Prognosis · Cancer-specific survival

Abbreviations

MpBC	Metaplastic breast cancer
TNBC	Triple-negative breast cancer
SEER	Surveillance, Epidemiology, and End Results
OS	Overall survival
BCSS	Breast cancer-specific survival
TN-MpBC	Triple-negative subtype of MpBC
Non-TN MpBC	MpBC without triple-negative subtype
HR	Hazard ratio
CI	Confidence interval
IDC	Invasive ductal carcinoma, no special type
ER	Estrogen receptor
PR	Progesterone receptor
HER2	Human epidermal growth factor receptor 2

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ICD-0-3	International Classification of Diseases for Oncology Version 3
TNBC	Triple-negative subtype of IDC
CT	Chemotherapy
RT	Radiotherapy

Introduction

Metaplastic breast cancer (MpBC) is a rare histologic subtype of breast cancer accounting for 0.25–2.0% of breast cancer diagnosis annually [1]. It consists of various combinations of mesenchymal, poorly differentiated ductal adenocarcinoma and other epithelial components [2]. The metaplastic breast cancer was not recognized as a distinct pathologic diagnosis until 2000. Since then, the incidence of MpBC has increased because of increasing recognition by pathologists [3]. However, there is a paucity of information on pathogenesis, optimal treatment, and clinical outcomes for MpBC because of rarity.

Invasive ductal carcinoma, no special type (IDC), is the most common type of breast cancer accounting for approximately 70–72% of all invasive breast cancers [4]. Previous studies have reported that MpBC is different from typical breast cancer and characterized by larger tumor size, less lymph node involvement, and poorer clinical outcomes than IDC [5, 6].

Among breast cancer patients, triple-negative breast cancer (TNBC) is a molecular subtype of breast cancer classified by low gene expression of estrogen receptor (ER), progesterone receptor (PR), and lack of human epidermal growth factor receptor 2 (HER2) gene amplification. It is well known that patients with TNBC have the tendency to relapse earlier and have shorter survival time than other molecular subtypes [7]. MpBC is generally poorly differentiated; ER , PR, and HER2 negative; and chemorefractory [8]. In current clinical practice, MpBC is treated similarly to other IDC according to molecular subtype despite the different clinicopathological features between MpBC and IDC [9]. In the current literature, the data about MpBC are largely based on small case series and single institution studies, and have yield confusing results [10–16]. Therefore, the prognostic significance of the metaplastic histological subtype and optimal treatment choices for MpBC is unclear.

The purpose of our study was to address this knowledge gap and to use a population wide database to compare the clinical course, tumor characteristics, and prognosis of MpBC with the subgroup of IDC that has the worst prognosis, i.e., triple-negative breast cancer (TNBC). We aim to examine the epidemiological evidence for MpBC as a histological breast cancer subtype with the worst prognosis, and evaluate molecular subtypes of MpBC for response to conventional breast cancer therapy.

Methods

Patients

The SEER database includes information of patient's age, race, marital status, cancer incidence, treatment, and survival, and it covers approximately 28% of the United States [17]. We used SEER data released in March 2017, which contains data from 18 population-based registries (1973–2014) and extracted data between 2010 and 2014. Since SEER started collected HER2 status in 2010, we chose 01/01/2010 as the starting point for our study. Data for tumor location, histology, and grade were recorded according to the International Classification of Diseases for Oncology Version 3 (ICD-0-3). The inclusion criteria were as follows: female, age of at least 18 years, breast cancer as first and the only cancer diagnosis, unilateral breast cancer, pathologic confirmation of invasive metaplastic carcinoma (ICD-0-3 8560, 8562, 8570–8573, 8575, 8980–8982) and invasive ductal carcinoma, not otherwise specified (IDC 8500), diagnosis not obtained from a death certification or autopsy, with information of known survival time, subtype and AJCC stage, stage exception of T0 and Tis. Then, we extract all cases with MpBC and triple-negative subtype of IDC (TNBC) as the study group. Finally, 22,433 patients were included, i.e., 1112 were diagnosed with MpBC and 21,321 with TNBC (Table 1).

Demographics and clinicopathological features

The demographic characteristics include age at diagnosis, race, and marital status; the clinicopathological characteristics include tumor grade, ER status, PR status, HER2 status, laterality, tumor size, lymph node status, distant metastases, AJCC stage, chemotherapy (CT), radiotherapy (RT), and local therapies. Tumor molecular subtype was analyzed as a binary categorical variable: triple negative (TN) versus non-TN (i.e., ER or PR+/HER2+, ER or PR+/HER2−, ER and PR−/HER2+).

ER status and PR status were classified according to immunohistochemistry (IHC) in SEER registry. If 1% or greater cells were stained positive in ER and PR tests, the result was considered positive. HER2 status positivity was defined as 3 + receptor overexpression on IHC staining and/or gene amplification on fluorescence in situ hybridization. Patients with ER, PR, and HER2 all negative were classified as TN.

The primary clinical outcome for analysis was overall survival (OS) from the date of diagnosis to the date of

Table 1 Stepwise inclusion and exclusion counts

Removal criterion	MpBC		IDC	
	Removed	Remaining	Removed	Remaining
2010–2014 IDC or MpBC patients	0 (0.00%)	1571	0 (0.00%)	227,214
Exclude patients whose disease is stage T0/Tis	4 (0.25%)	1567	244 (0.11%)	226,970
Exclude men	2 (0.13%)	1565	1960 (0.86%)	225,010
Exclude patients younger than 18 years	0 (0.00%)	1565	2 (0.00%)	225,008
Exclude patients without histology or cytology confirmation	1 (0.00%)	1564	231 (0.10%)	224,777
Exclude patients whose tumor was not the first tumor	307 (19.6%)	1257	41,309 (18.38%)	183,468
Exclude patients with bilateral involvement	1 (0.00%)	1256	147 (0.00%)	183,321
Exclude patients without survival information/diagnosed by autopsy/death record only	33 (2.63%)	1223	4886 (2.67%)	178,435
Exclude patients with unknown molecular subtype	89 (7.28%)	1134	11,827 (6.63%)	166,608
Exclude patients with unknown AJCC stage	22 (1.94%)	1112	3053 (1.83%)	163,555
Removal criterion	MpBC		TNBC	
	Removed	Remaining	Removed	Remaining
Final data set	0 (0.00%)	1112	142,234 (87.0%)	21,321

MpBC metaplastic breast cancer, *IDC* invasive ductal carcinoma, no special type, *TNBC* triple-negative breast cancer

death for any cause, and the secondary outcome was breast cancer-specific survival (BCSS) from the date of diagnosis to the date of death caused by breast cancer. Patients who were not known to have died were censored at the time duration from the diagnosis of cancer to the last follow-up date. The SEER released in March 2017 contains complete death date through 2014. Therefore, our study cut-off date is December 31, 2014.

Statistical analysis

Demographic, clinicopathological, and treatment-related variables were compared between MpBC and non-MpBC TNBC by Pearson Chi-square test for categorical nominal data. Kaplan–Meier method was used to analyze OS rates with log-rank test to determine statistical differences across groups. Prognostic factors for OS were also evaluated by multivariate Cox proportional hazard models. Fine-Gray competing risk analysis and multivariate regression model of competing risk were used to evaluate prognostic factors for BCSS [18, 19].

Hazard ratios (HRs) were reported with their 95% confidence intervals (CIs).

All statistical analyses and charts of survival probabilities were performed using the SPSS 22.0 (IBM Corporation, Armonk, NY, USA) and R statistical software (version 3.4.3, R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/). A P value < 0.05 was considered statistically significant in all analysis.

Results

Patient, clinical, and tumor characteristics and incidence of metaplastic breast cancer

From SEER database, we identified a total of 312,045 breast cancer patients from 2010 to 2014, which included 1571 MpBC patients, 227,214 IDC patients, and 83,260 patients with other pathological subtypes. Finally, a total of 22,433 eligible breast cancer patients during 2010–2014 were analyzed in our study: 1112 MpBC and 21,321 TNBC (Table 1).

Patient demographics, tumor characteristics, and local therapies are summarized in Table 2 for MpBC and TNBC. Among MpBC, there were 763 (68.6%) TN-MpBC and 349 (31.4%) non-TN MpBC. This high proportion of TN molecular subtype is obviously different from the most common IDC of the breast, only 15–20% of which are TN. Despite the high proportion of MpBC being TN, there were significantly differences between MpBC and non-MpBC TNBC including age of diagnosis, nuclear grade, size, and lymph node status (Table 2). Compared with the non-MpBC TNBC group, MpBC patients were older at diagnosis (≥ 50 years, 79.6%

Table 2 Patient, tumor, and treatment-related characteristics in metaplastic breast cancer (MpBC) and the triple negative of invasive ductal carcinoma not otherwise specified (TNBC)

Characteristic	MpBC ($n=1112$)		TNBC ($n=21,321$)		P*
	n	%	n	%	
Age					< 0.001
18–49 years	227	20.4	6430	30.2	
≥ 50 years	885	79.6	14,891	69.8	
Race					0.007
Black	185	16.6	4443	20.8	
White	837	75.3	15,162	71.1	
Other	86	7.7	1608	7.5	
Unknown	4	0.4	108	0.5	
Marital status					0.001
Married	552	49.6	11,455	53.7	
Unmarried	514	46.2	8727	40.9	
Unknown	46	4.1	1139	5.3	
Tumor grade					< 0.001
Well/moderately	188	16.9	3504	16.4	
Poorly/undifferentiated	797	71.7	17,131	80.3	
Unknown	127	11.4	686	3.2	
Molecular subtype					< 0.001
Triple negative (TN)	763	68.6	21,321	100.0	
Non-triple negative					
HER2+/HR+	28	2.5	0	0.0	
HER2+/HR−	41	3.7	0	0.0	
HER2−/HR+	280	25.2	0	0.0	
Laterality					0.372
Left	547	49.2	10,929	51.3	
Right	565	50.8	10,389	48.7	
Unknown	0	0.0	3	0.0	
Tumor size					< 0.001
≤ 2 cm	278	25.0	9208	43.2	
> 2 cm	824	74.1	11,831	55.5	
Unknown	10	0.9	282	1.3	
T stage					< 0.001
T1	278	25.0	9100	42.7	
T2/T3	731	65.7	10,787	50.6	
T4	99	8.9	1335	6.3	
Tx	4	0.4	99	0.5	
Node status					< 0.001
Negative	837	75.3	13,441	63.0	
Positive	269	24.2	7810	36.6	
Unknown	6	0.5	70	0.3	
Metastasis					0.960
M0	1052	94.6	20,178	94.6	
M1	60	5.4	1143	5.4	
AJCC stage					< 0.001
I	248	22.3	7560	35.5	
II/III	804	72.3	12,618	59.2	
IV	60	5.4	1143	5.4	

Table 2 (continued)

Characteristic	MpBC ($n=1112$)		TNBC ($n=21,321$)		P*
	n	%	*n*	%	
Sites of metastasis					< 0.001
Bone-only metastasis	7	11.7	228	19.9	
Brain-only metastasis	2	3.3	29	2.5	
Liver-only metastasis	2	3.3	111	9.7	
Lung-only metastasis	25	41.7	211	18.5	
Multiple or other lesion metastatic sites	24	40.0	564	49.3	
Radiation therapy					0.024
None/unknown	602	54.1	10,805	50.7	
Done	510	45.9	10,516	49.3	
Chemotherapy					< 0.001
None/unknown	383	34.4	5113	24.0	
Done	729	65.6	16,208	76.0	
Primary lesion surgery					0.001
No	53	4.8	1597	7.5	
Yes	1059	95.2	19,688	92.3	
Unknown	0	0.0	36	0.2	
Distant lesion surgery					0.075
No	1096	98.6	20,800	97.6	
Yes	16	1.4	490	2.3	
Unknown	0	0.0	31	0.1	

*P value for the comparison of variable between MpBC and TNBC

vs. 69.8%, $P<0.001$), had larger tumor size (> 2 cm, 74.1% vs. 55.5%, $P<0.001$), and had less lymph node metastasis (negative, 75.3% vs. 63.0%, $P<0.001$). Although there was no significant difference in the rate of distant metastasis (M1, 5.4% vs. 5.4%, $P=0.960$), the most common site of distant metastases in MpBC was the lung while in non-MpBC TNBC it was the bone (41.7 and 19.9%, respectively, $P<0.001$). About treatment options, patients with MpBC were more likely to undergo primary lesion surgery but less likely to receive chemotherapy and radiotherapy compared with non-MpBC TNBC patients (all Ps < 0.001).

Survival

In our study, the median follow-up time was 24, 22, and 21 months in TNBC, TN-MpBC, and non-TN MpBC group. There were 2595 (12.2%) tumor-related death events observed in TNBC group, and 132 (17.3%) in TN-MpBC group, 51 (14.6%) in non-TN MpBC group. The death for other cause was observed in 663 (3.1%), 26 (3.4%), and 7 (2.0%) in TNBC, TN-MpBC, and non-TN MpBC groups, respectively.

Clinicopathological factors were analyzed by univariate analysis for association with BCSS and OS. The P values of the comparisons along with the 3-year survival rates were reported in Table 3. The 3-year OS rate was 76.3% in MpBC patients who received chemotherapy versus 70.3% in patients not treat with chemotherapy, and chemotherapy was significantly ($P=0.025$) associated with superior OS in MpBC on univariate analysis (Supplementary Table). Other prognostic factors investigated for OS included age, nuclear grade, AJCC stage, primary lesion surgery, and radiotherapy. The 3-year OS in MpBC receiving radiotherapy was 82.4% compared to 66.7% in those without radiotherapy, and radiotherapy is also a significant ($P<0.001$) prognostic factor for OS in univariate analysis.

MpBC had worse clinical outcomes than non-MpBC TNBC both in BCSS and OS (both $P<0.001$). The 3-year BCSS rate was 78.1% in MpBC and 83.8% in non-MpBC TNBC, and the 3-year OS rate was 74.2% in MpBC and 80.0% in non-MpBC TNBC. In MpBC group, patients with triple-negative subtype had worse prognosis. The 3-year BCSS rate was 77.3% in TN MpBC and 79.9% in non-TN MpBC, and the 3-year OS rate was 73.1 and 76.8% in TN MpBC and non-TN MpBC, respectively. Furthermore, TN-MpBC has worse prognosis than non-MpBC TNBC both in BCSS and OS while the BCSS and OS of non-TN MpBC were not statistically different from those of non-MpBC TNBC (Figs. 1, 2; Table 4). After adjusting for age, tumor size, node status, metastasis, chemotherapy, radiotherapy, and primary lesion surgery, the TN-MpBC patients had worst prognosis [vs. TNBC (reference); HR 1.429; 95% CI 1.214–1.681; $P<0.001$] in OS, and [vs. TNBC (reference); HR 1.710; 95% CI 1.428–2.050; $P<0.001$] in BCSS. There was no statistical difference in OS ($P=0.197$) and BCSS ($P=0.970$) among patients with TNBC and non-TN MpBC.

To further explore the effect of chemotherapy and radiotherapy on survival in different molecular subtypes of MpBC, univariate analysis and multivariate analysis were conducted comparing TN-MpBC and non-TN MpBC. In Kaplan–Meier analysis, chemotherapy (CT) was not associated with significant difference in OS of TN-MpBC (Fig. 3a). In non-TN MpBC group, the 3-year OS was 79.8% for patients receiving chemotherapy and 70.5% in patients without chemotherapy, and CT was associated ($P=0.033$) with improved OS (Fig. 3b). In contrast, radiotherapy (RT) was associated with improved OS in both TN-MpBC ($P=0.0031$, Fig. 3c) and non-TN MpBC ($P=0.0024$, Fig. 3d). Using proportional hazard-based methods, univariate and multivariate regression models were designed a priori to adjust for relevant clinicopathological factors in MpBC patients. Radiotherapy was associated with improved OS and BCSS in MpBC in univariate analyses and in multivariate analyses (Table 5). In contrast, chemotherapy was

Table 3 Univariate analysis of the breast cancer-specific survival (BCSS) and overall survival (OS) of the study cohort

	n	3-year BCSS (%)	*P*	3-year OS (%)	*P*
Pathology			< 0.001		< 0.001
TNBC	21,321	83.8		80.0	
MpBC	1112	78.1		74.2	
TN-MpBC	763	77.3		73.1	
Non-TN MpBC	349	79.9		76.8	
Age (years)			0.040		< 0.001
18–49	6657	83.7		82.3	
≥ 50	15,776	83.4		78.7	
Race			< 0.001		< 0.001
Black	4628	79.7		75.5	
White	15,999	84.2		80.5	
Other	1694	86.2		83.4	
Unknown	112	97.6		95.4	
Tumor grade			< 0.001		< 0.001
Well/moderately	3692	87.8		83.8	
Poorly/undifferentiated	17,928	82.9		79.3	
Unknown	813	76.2		71.6	
Tumor size			< 0.001		< 0.001
≤ 2 cm	9486	92.9		90.2	
> 2 cm to ≤ 5 cm	9965	82.9		78.7	
> 5 cm	2690	57.8		52.6	
Unknown	292	36.6		29.8	
Node status			< 0.001		< 0.001
Negative	14,278	92.1		88.8	
Positive	8079	69.0		64.7	
Unknown	76	22.8		14.1	
Metastasis			< 0.001		< 0.001
No metastasis	21,230	87.0		83.4	
Metastases	1203	20.1		15.0	
AJCC stage			< 0.001		< 0.001
I	7808	96.0		93.3	
II/III	13,422	81.8		77.5	
IV	1203	20.1		15.0	
Radiation therapy			< 0.001		< 0.001
None/unknown	11,407	80.9		75.9	
Done	11,026	86.1		83.6	
Chemotherapy			0.3852		< 0.001
None/unknown	5496	84.1		75.5	
Done	16,937	83.2		81.1	
Primary lesion surgery			< 0.001		< 0.001
No	1650	43.4		36.3	
Yes	20,747	86.3		82.8	
Unknown	36	62.2		59.5	
Distant lesion surgery			< 0.001		< 0.001
No	21,896	83.7		79.9	
Yes	506	73.6		71.9	
Unknown	31	80.7		73.8	

BCSS breast cancer-specific survival, *OS* overall survival

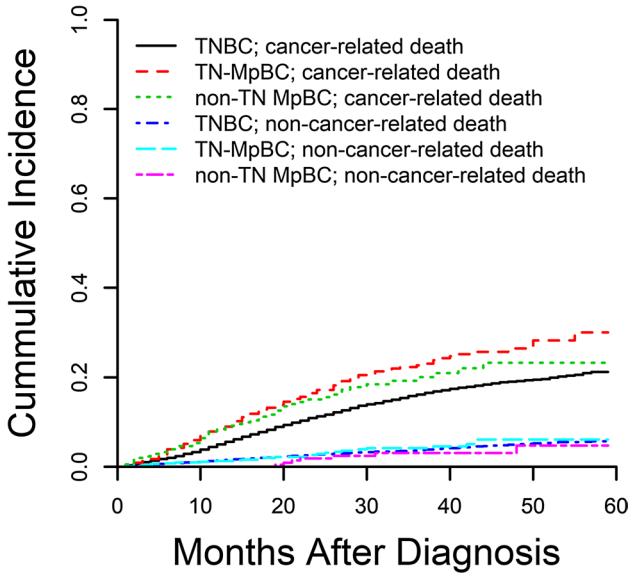

Fig. 1 Cumulative incidence of patients with MpBC and TNBC by competing risk analysis. *TN-MpBC* triple-negative subtype of metaplastic breast cancer, *TNBC* triple-negative breast cancer, *non-TN MpBC* metaplastic breast cancer without triple-negative subtype

only associated with improved OS in univariate analysis and not in multivariate analysis for OS and analysis for BCSS.

Therefore, MpBC was highly resistant to therapy, especially the TN MpBC in which chemotherapy was not associated with improved OS or BCSS and radiotherapy was associated with improved OS but not BCSS.

Discussion

MpBC is a heterogeneous neoplasm which may contain different components of carcinoma, sarcomatoid carcinoma, spindle cell carcinoma, or pseudosarcoma. Prognostic studies have explored the outcomes of this rare malignancy and showed conflicting results [10–16]. Barquet-Munoz et al. did not find differences in OS nor disease-free survival between MpBC and other breast cancer subtypes [13]. Overall, MpBC appears to be more aggressive than the typical invasive ductal carcinoma of the breast [14, 15], and particularly TNBC [10, 16]. However, all but one study published to date are limited by small sample sizes, and most of them lacked information about how the different molecular subtypes of MpBC may influence prognosis. Nelson et al. analyzed data

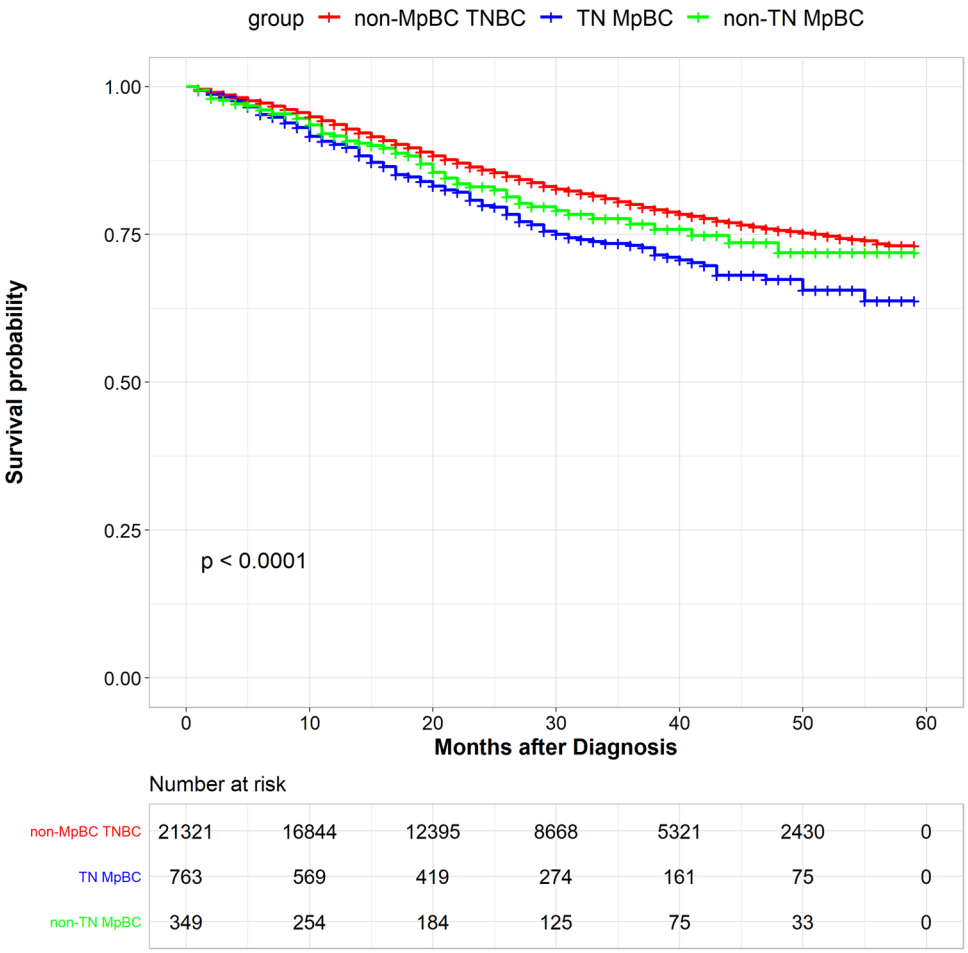

Fig. 2 BCSS and OS Among patients with TN-MpBC, non-TN MpBC, and non-MpBC TNBC. *non-MpBC TNBC* triple-negative subtype of breast cancer other than metaplastic breast cancer, *TN-MpBC* triple-negative subtype of metaplastic breast cancer, *non-TN MpBC* non-triple-negative subtype of metaplastic breast cancer, *BCSS* breast cancer-specific survival, *OS* overall survival

Table 4 Prognostic factors for overall survival (OS) and breast cancer-specific survival (BCSS) in our study cohort by multivariate analyses

	OS		BCSS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Group				
TNBC	1.0 [reference]		1.0 [reference]	
TN-MpBC	1.429 (1.214–1.681)	< 0.001	1.710 (1.428–2.050)	< 0.001
Non-TN MpBC	0.842 (0.649–1.093)	0.197	1.010 (0.715–1.410)	0.970
Age				
18–49 years	1.0 [reference]		1.0 [reference]	
≥ 50 years	1.379 (1.274–1.492)	< 0.001	1.180 (1.075–1.280)	< 0.001
Tumor size				
≤ 2 cm	1.0 [reference]		1.0 [reference]	
2 cm to ≤ 5 cm	1.891 (1.725–2.072)	< 0.001	1.840 (1.650–2.060)	< 0.001
> 5 cm	3.379 (3.035–3.762)	< 0.001	3.380 (2.965–3.850)	< 0.001
Unknown	3.688 (3.081–4.414)	< 0.001	3.270 (2.547–4.190)	< 0.001
Node status				
Negative	1.0 [reference]		1.0 [reference]	
Positive	2.446 (2.260–2.647)	< 0.001	2.740 (2.485–3.010)	< 0.001
Unknown	2.709 (2.054–3.572)	< 0.001	2.790 (1.911–4.090)	< 0.001
Metastasis				
No metastasis	1.0 [reference]		1.0 [reference]	
Metastasis	4.333 (3.927–4.780)	< 0.001	4.610 (4.079–5.200)	< 0.001
Radiotherapy				
None/unknown	1.238 (1.151–1.331)	< 0.001	1.200 (1.105–1.310)	< 0.001
Done	1.0 [reference]		1.0 [reference]	
Chemotherapy				
None/unknown	2.136 (1.977–2.309)	< 0.001	1.460 (1.315–1.620)	< 0.001
Done	1.0 [reference]		1.0 [reference]	
Primary lesion surgery				
Yes	1.0 [reference]		1.0 [reference]	
No	2.241 (2.032–2.471)	< 0.001	2.190 (1.937–2.480)	< 0.001
Unknown	1.948 (1.044–3.636)	0.036	1.480 (0.553–3.950)	0.440

HR Hazard ratio, *CI* confidence interval, *BCSS* breast cancer-specific survival, *OS* overall survival

from 2001 to 2010 in the SEER database that contained 1011 MpBC patients [15], and they were not able to analyze TN-MpBC because the HER2 status was not included in the SEER data in that time period. The recent release of data that included HER2 status in the SEER database offers a unique opportunity to compare the prognosis of patients with MpBC subtypes versus other TNBC, and explore the role of chemotherapy and radiotherapy in this setting. There is no consistent immune-phenotype or specific markers that define MpBC in clinical practice [20]. It is therefore of great interest to define MpBC subgroups and investigate whether molecular subtyping has a prognostic role in MpBC.

Because of the rarity of MpBC, the current larger studies are all based on cancer database such as National Cancer Database and SEER database [15, 21]. The SEER Program of the National Cancer Institute (NCI) is an authoritative source of information on cancer and is the only comprehensive source of population-based information in the United States. Within SEER data, the International Classification of Disease-Oncology (ICD-0-3) was used to code the primary site and histologic type for cases diagnosed since 2001. The SEER program performs continuous quality control activity to ensure the collection of high-quality data. Our analysis was performed on only histologically confirmed patients with MpBC to make the results more reliable.

TNBC is associated with the worst prognosis among all molecular subtypes of breast cancer, with a median survival of 10–13 months once metastases were detected [22]. Because of rarity of MpBC, the available data about prognosis between different subgroups of MpBC and non-MpBC TNBC were limited and conflicting [13, 16, 23]. The largest MpBC cohort in these studies was 47 [16]. In contrast, among our study cohort of 1112 eligible patients with MpBC, 763 patients are TN and 349 are non-TN.

Pezzi et al. conducted a retrospective study of 892 MpBC cases in 2007, and found that MpBC patients presented with

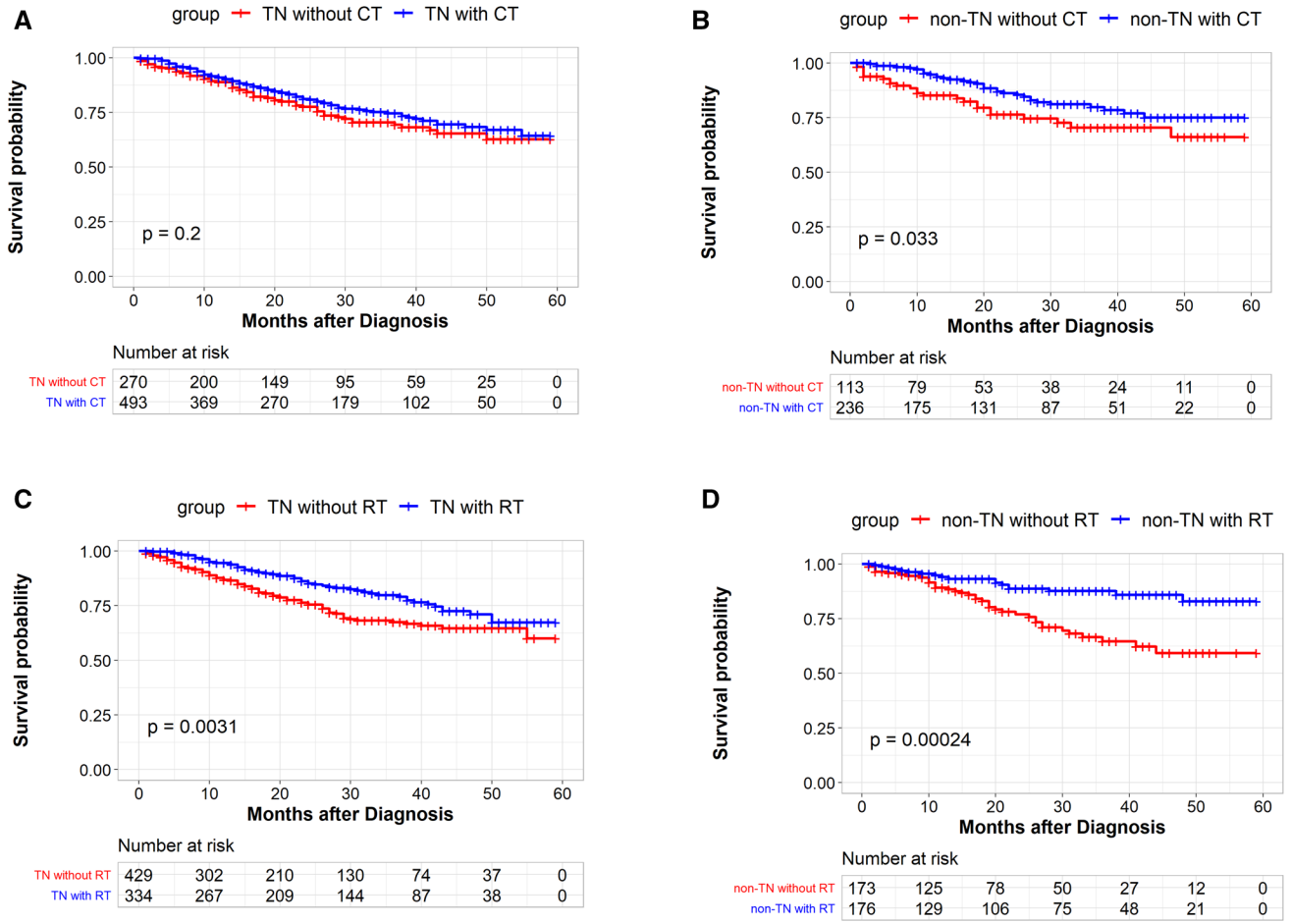

Fig. 3 OS among MpBCs with or without chemotherapy or radiotherapy by subtype. *TN* triple-negative subtype, *non-TN* without triple-negative subtype, *CT* chemotherapy, *RT* radiotherapy, *BCSS* breast cancer-specific survival, *OS* overall survival. **a** TN-MpBC with or without chemotherapy, **b** non-TN MpBC with or without chemotherapy, **c** TN-MpBC with or without radiotherapy, **d** non-TN MpBC with or without radiotherapy

fewer T1 tumors, less lymph node involvement, and fewer ER-positive tumors than IDC group [21]. Their results were consistent with our results about MpBC and TNBC. Despite less lymph node involvement at presentation, we found that MpBC had worse prognosis than non-MpBC TNBC in both OS and BCSS, and would dethrone and replace TNBC as the breast cancer subtype with the worst prognosis. Molecular subtyping was relevant in MpBC prognosis. Although non-TN MpBC was not statistically different from that of non-MpBC TNBC, TN MpBC had worse prognosis than non-TN MpBC, i.e., the worse of the worst prognosis. In this study, we found that the MpBC group was more likely to receive primary lesion surgery and receive less chemotherapy and radiotherapy than the non-MpBC TNBC group. Chemotherapy is the mainstay of systematic therapy for TNBC, and thus the proportion of TNBC treated with chemotherapy was high. Patients with MpBC were less likely to have lymph node metastases and thus received less radiotherapy. A previous study of SEER data from 1988 to 2006 found that radiotherapy was associated with improved survival in MpBC [24]. Molecular subtyping of MpBC may be relevant to response to therapy as we found that while both chemotherapy and radiotherapy were associated with improved prognosis in non-TN MpBC, radiotherapy but not chemotherapy was associated with improvement in TN MpBC. These results confirmed the previous report by Tseng et al. about radiotherapy [24] and might also suggest that the benefit of chemotherapy in TN-MpBC was limited. A recent study has implicated that MpBCs with HER2-positive subtype may have favorable outcomes in early-staged and locally advanced MpBC. They emphasize the role of HER2-targeted therapy in MpBC and different prognosis in various stages [25]. However, our study has explored the prognosis and role of different treatments in different subtypes of MpBCs. We aim to further select a subgroup of MpBC which can benefit more from aggressive treatments, improve our understanding of MpBC, and lead to more individualized therapies for breast cancer.

Table 5 Prognostic factors for overall survival (OS) and breast cancer-specific survival (BCSS) in metaplastic breast cancer (MpBC) by univariate and multivariate analyses

	OS				BCSS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age								
18–49 years	1.0 [reference]		1.0 [reference]		1.0 [reference]		1.0 [reference]	
≥ 50 years	1.648 (1.127–2.411)	0.010	1.643 (1.112–2.427)	0.013	1.440 (0.974–2.12)	0.068	1.524 (0.997–2.330)	0.052
Tumor size								
≤ 2 cm	1.0 [reference]		1.0 [reference]		1.0 [reference]		1.0 [reference]	
> 2 cm to ≤ 5 cm	2.407 (1.482–3.911)	< 0.001	2.054 (1.255–3.360)	0.004	2.480 (1.420–4.320)	0.001	2.034 (1.152–3.590)	0.014
> 5 cm	7.672 (4.749–12.395)	< 0.001	5.762 (3.492–9.509)	< 0.001	8.970 (5.220–15.420)	< 0.001	6.253 (3.514–11.130)	< 0.001
Unknown	5.99 (1.779–20.171)	0.004	1.769 (0.496–6.311)	0.380	8.090 (1.910–34.340)	0.005	2.540 (0.695–9.280)	0.16
Node status								
Negative	1.0 [reference]		1.0 [reference]		1.0 [reference]		1.0 [reference]	
Positive	2.387 (1.809–3.150)	< 0.001	1.502 (1.097–2.056)	0.011	2.570 (1.920–3.450)	< 0.001	1.435 (1.011–2.040)	0.043
Unknown	29.55 (12.876–67.835)	< 0.001	10.017 (3.967–25.295)	< 0.001	10.380 (2.460–43.740)	0.001	2.925 (0.627–13.660)	0.17
Metastasis								
No metastasis	1.0 [reference]		1.0 [reference]		1.0 [reference]		1.0 [reference]	
Metastasis	9.204 (6.596–12.843)	< 0.001	3.342 (2.238–4.990)	< 0.001	10.100 (6.950–14.700)	< 0.001	3.942 (2.442–6.360)	< 0.001
Molecular subtype								
Triple negative	1.229 (0.910–1.661)	0.178	1.558 (1.140–2.212)	0.006	1.150 (0.833–1.590)	0.400	1.446 (0.989–2.120)	0.057
Non-triple negative	1.0 [reference]		1.0 [reference]		1.0 [reference]		1.0 [reference]	
Radiotherapy								
None/unknown	1.874 (1.416–2.478)	< 0.001	1.544 (1.148–2.078)	0.004	1.710 (1.270–2.300)	< 0.001	1.474 (1.067–2.040)	0.019
Done	1.0 [reference]		1.0 [reference]		1.0 [reference]		1.0 [reference]	
Chemotherapy								
None/unknown	1.361 (1.038–1.786)	0.026	1.271 (0.950–1.699)	0.106	1 0.000 (0.738–1.370)	0.980	0.961 (0.682–1.360)	0.820
Done	1.0 [reference]		1.0 [reference]		1.0 [reference]		1.0 [reference]	
Primary lesion surgery								
No	5.470 (3.642–8.213)	< 0.001	2.639 (1.647–4.228)	< 0.001	5.740 (3.690–8.920)	< 0.001	2.446 (1.332–4.490)	< 0.001
Yes	1.0 [reference]		1.0 [reference]		1.0 [reference]		1.0 [reference]	

HR Hazard ratio, *CI* confidence interval, *BCSS* breast cancer-specific survival, *OS* overall survival

The transcriptomic profiles of MpBC are most closely related to claudin-low cancers, a novel subset of TNBC characterized by loss of genes involved in cell–cell adhesion and apical-basal polarity [26]. Previous study has reported that majority of claudin-low group are MpBC [27]. MpBC were also found to be enriched with stem cell-like gene signature similar to claudin-low cancers [28]. Claudin-low tumors are enriched in epithelial-to-mesenchymal transition (EMT) and stem-like features which can provide an explanation for the aggressive phenotype of MpBC and poor prognosis of TN-MpBC [27, 29]. However, the prognosis of claudin-low breast cancer does not agree with the prognosis of MpBC that we observed from the SEER data. The prognosis of claudin-low breast cancers resembles that of a poor prognosis and good responder subtype (basal and HER2 subtype) [30], but the prognosis of MpBC was the worst in breast

cancer. The molecular mechanism underlying the potential lack of response to chemotherapy for TN-MpBC also needs further investigation.

The National Comprehensive Cancer Network clinical practice guidelines recommend that MpBC should be treated in the same fashion as other invasive breast cancer such as TNBC [31]. Because of rarity of MpBC, the chance to conduct clinical trials in this patient population is limited. The role of surgical resection, chemotherapy, radiotherapy, and their combinations in the management of MpBC is not yet clear. Warren et al. found that radiotherapy after lumpectomy and mastectomy can improve OS but not disease-specific survival (DSS) in MpBC [24]. Our finding that radiotherapy was associated with improved OS and BCSS for MpBC was consistent with their finding.

Limitations

The HER2 status was not available in the SEER database until 2010. Therefore, the follow-up time was not very long. Moreover, the SEER database does not provide information about adjuvant or neoadjuvant chemotherapy, targeted therapy, menopause status, genomic and transcriptomic information, disease recurrence, or recurrent sites. There are some patients with no clear evidence of receiving chemotherapy and/or radiotherapy in our study as coded as such in the SEER database. We grouped this population into patients with no therapy although this may diminish the statistical effects of the categorical variables (chemotherapy and radiotherapy).

Conclusions

Despite the above limitations, our study has taken a step in defining the prognosis of MpBC with different subtypes. TN MpBC had the worst outcomes both in BCSS and OS compared with non-MpBC TNBC while the prognosis of non-TN MpBC is not different from that of TNBC. Radiotherapy and chemotherapy were both associated with improved prognosis in non-TN MpBC. In contrast, chemotherapy was not associated with improved prognosis in TN MpBC. Improving our understanding of the clinical features of this rare subtype of breast cancer is the first step. Further studies including multi-omics analysis of breast cancer should be undertaken to search for more effective therapy and perhaps more individualized therapies for MpBC.

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Compliance with ethical standards

Conflict of interest Dr. Yeung is the principal investigator of an investigator-initiated clinical trial supported by DepoMed and a retrospective clinical study supported by Bristol-Myer Squibb through ARISTA-USA (BMS/Pfizer American Thrombosis Investigator Initiated Research Program). The support granted by commercial companies was not used in support of the current study. All other authors declare no competing financial or non-financial interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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