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Survival trends of patients with metaplastic breast carcinoma with different hormone receptor statuses: a SEER-based retrospective cohort study

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Abstract

Background Metaplastic breast carcinoma (MpBC) is a rare histological subtype of breast cancer, and its prognosis is relatively poor. The survival trend of MpBC with different hormone receptor statuses has remained unclear over the past two decades.

Methods MpBC patient data were collected from the Surveillance, Epidemiology, and End Results database from 2000 to 2019. Patients were divided into two groups according to their hormone receptor status (negative and positive). The survival probabilities were calculated via Kaplan–Meier curves. Logistic regression analysis was used to obtain odds ratios for treatment and demographic characteristics. Multivariate Cox regression was used to identify prognostic factors.

Results A total of 3,076 patients were enrolled, and a significant improvement in survival was observed over the last 10 years. For HR-negative MpBC patients, both overall survival and breast cancer-specific survival improved, whereas no survival improvement was observed for HR-positive patients. Compared with those in the time period from 2000 to 2009, the proportion of negative nodes and the likelihood of receiving chemotherapy increased for HR-negative patients from 2010 to 2019. In the HR-negative subgroup, the survival of Whites improved significantly, whereas the survival of Blacks improved in the HR-positive subgroup.

Conclusions The survival of HR-negative MpBC patients has improved significantly in the past 20 years, which may be related to early diagnosis, increased adjuvant therapy and medical development, but no trend towards improvement has been observed in HR-positive patients. Racial disparities in different HR statuses also need to be addressed.

Keywords Metaplastic breast carcinoma, Survival trends, Hormone receptor status, Overall survival, Breast cancer-specific survival, Race disparities

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Introduction

Huevos was the first to describe metaplastic breast carcinoma (MpBC) [1]. It is a rare histological subtype of malignant breast tumour, accounting for approximately 0.2–2.0% of all breast cancer diagnoses [2–4]. The World Health Organization (WHO) classified MpBC as a type of heterogeneous tumour in 2000, including spindle cell carcinoma, squamous cell carcinoma, MpBC with mesenchymal differentiation, fibromatosis-like metaplastic carcinoma, and low-grade adenosquamous carcinoma [5]. MpBC is characterized by a larger tumour size, less lymph node metastasis, higher histology grade, and worse prognosis [5–7].

There are no association-endorsed treatment guidelines specific to the management of MpBC, with only limited evidence for the efficacy of MpBC treatment. Currently, the available literature includes case reports, retrospective studies conducted at certain single centres, and analyses based on large databases. The National Comprehensive Cancer Network (NCCN) recommends the use of invasive carcinoma guidelines for the management of MpBC, with surgical treatment as the first choice, combined with adjuvant therapy based on clinicopathological characteristics and staging of the tumour [8].

Most MpBC patients are identified as having triple-negative breast cancer (TNBC) because of a lack of expression of oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). However, there are also a small number of hormone receptor (HR)-positive and HER2-positive cases. HR positivity is considered a biomarker of better outcomes for nonspecific types of breast cancer, but HR positivity status is not associated with better survival in MpBC, which is different from invasive ductal carcinoma (IDC) and lobular carcinomas [9].

The past few decades have witnessed exciting advances in the integrated treatment of breast cancer, but the impact of these advances on MpBC patients with different HR statuses remains unclear. The primary objective of this study was to identify changes in survival trends in MpBC patients with different HR statuses over the past two decades and to determine whether survival differences exist among different races.

Materials and methods

Study population

All data were extracted from the Surveillance, Epidemiology, and End Results (SEER) Program (Incidence - SEER Research Plus Data, 17 Registries, Nov 2021 Sub (2000–2019)) via SEER-stat software (SEER*Stat 8.4.0.1). Patients who were diagnosed with pathologically confirmed MpBC between 2000 and 2019 were enrolled in the study. The selection criteria for identifying eligible patients were as follows: (1) female and (2) site-recoded rare tumours (19.5 metaplastic carcinomas of the breast). Among the patients selected, those with the following situations were excluded: (1) unknown hormone receptor status; (2) distant metastasis or unknown metastatic status; (3) AJCC T stage was unknown; (4) no surgery, unknown whether surgery was performed or an unknown surgical approach was used; (5) more than one primary tumour; (6) unknown unilateral or bilateral side; (7) survival time less than one month; and (8) unknown race or ethnicity (Supplementary Information Fig. 1).

Cohort definition and clinicopathological characteristics

The entire cohort was divided into two groups according to their HR status: HR-negative (ER-negative and PR negative) and HR-positive (ER-positive and/or PR positive). The following variables were recorded to describe the characteristics of the patients: age, marital status, race, T stage, tumour grade, year of diagnosis, HER2 status, lymph node status, chemotherapy, radiotherapy and mastectomy type. Race/ethnicity was categorized as White, Black, Hispanic or Other (American Indian/AK Native, Asian/Pacific Islander). Marriage status was categorized as married or unmarried, including divorced, separated, unmarried or domestic partner, single or widowed) and unknown. The tumour grade was classified as I (grade I, well differentiated, differentiated, NOS), II (grade II, moderately differentiated, intermediate differentiation), III/IV (grade III, poorly differentiated; grade IV, undifferentiated; anaplastic) or unknown. HER2 status was categorized as positive or negative, and missing or borderline HER2 status was categorized as borderline/unknown. Mastectomy was defined according to the SEER codes for 'subcutaneous mastectomy', 'total (simple) mastectomy NOS', 'modified radical mastectomy', 'radical mastectomy NOS', 'extended radical mastectomy', and 'mastectomy, NOS'. Breast conserving surgery (BCS) was defined as codes for 'partial mastectomy, NOS' or 'less than total mastectomy, NOS' (including partial mastectomy with nipple resection, lumpectomy or excisional biopsy, re-excision of the biopsy site for gross or microscopic residual disease, and segmental mastectomy).

Statistical analysis

Pearson's chi-square test was used to compare patient characteristics between the two groups. A linear-by-linear association test was adopted to evaluate trends in the proportion of hormone receptor status of metaplastic breast cancer patients over the study period. Survival outcomes, including overall survival (OS) and breast cancer-specific survival (BCSS), were examined via the Kaplan–Meier method and compared between the two groups via log-rank tests. The Cox proportional hazard model was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for both OS and BCSS. Finally,

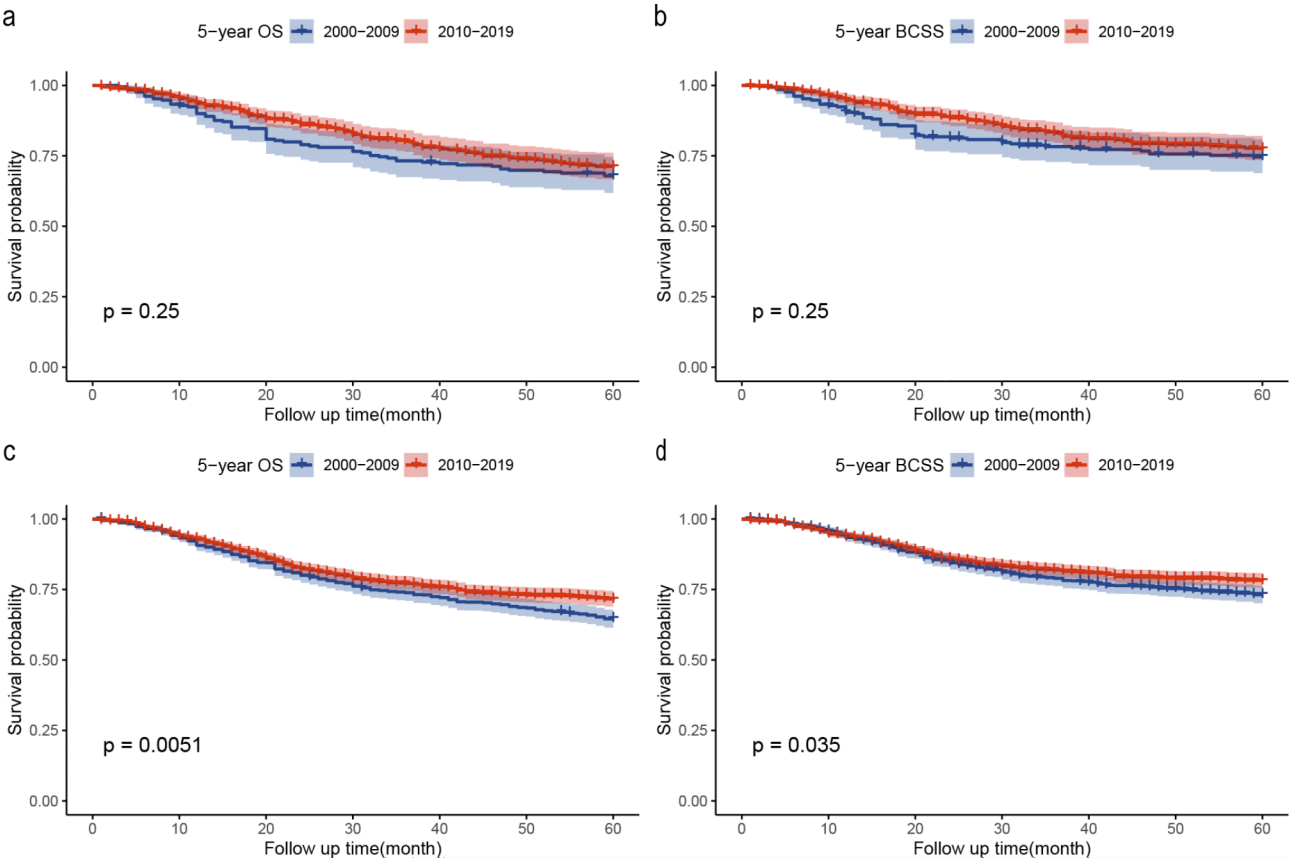

Fig. 1 Survival trends of metaplastic breast cancer patients with different hormone receptor statuses. (**a**, **b**) Five-year overall survival and breast cancer-specific survival of hormone receptor-positive patients; (**c**, **d**) five-year overall survival and breast cancer-specific survival of hormone receptor-negative patients. P values were determined via the univariate log-rank test

multivariable logistic regression analysis adjusting for the same demographic and clinical covariates was used to obtain odds ratios (ORs) of treatment options in the time periods for different HR statuses of MpBC patients. All tests were two-sided, and a P value <0.05 was used to indicate statistical significance. All of the analyses were performed with R statistical software (version 4.1.1).

Results

Baseline characteristics

A total of 3,076 female MpBC patients were identified through the SEER database from 2000 to 2019. More than half of them were ≥50 years old ($n=2363$, 76.8%), with the following detailed information: White race ($n=1993$, 64.8%), married ($n=1581$, 51.4%), grade III&IV ($n=2168$, 70.5%), T2 stage ($n=1562$, 50.8%), negative lymph nodes ($n=2215$, 72.0%) and HR-negative ($n=2320$, 75.4%). There was a linear decrease in the HR-negative proportion within the year of diagnosis (Supplementary Information Fig. 2). A total of 1,079 patients with a median age of 61 (21–99) years were enrolled in the 2000–2009 group, and the median follow-up time was 124 (1–239) months. A total of 1,997 patients were assigned to the 2010–2019 group, with a median age of 61 (22–100) years and a median follow-up time of 34 (1-119) months.

There were statistically significant differences in demographic and pathological characteristics, including race/ethnicity, HR status, and lymph node status, between the two groups (all $p<0.05$, Table 1). Compared with those in the 2000, patients were more likely to receive chemotherapy (67.9% vs. 59.0%) and radiotherapy (50.9% vs. 45.1%) (Table 1).

Survival trends of all patients

Survival improved in both groups (Supplementary Fig. 3), with 5-year OS rates ranging from 65.23 to 71.19% ($p=0.0018$) and 5-year BCSS rates ranging from 73.44 to 77.85% ($p=0.014$). There were no differences in survival between HR-positive and HR-negative patients ($p>0.05$, Supplementary Fig. 4). In terms of survival, HR-positive patients showed no improvement in the 5-year OS rate (67.93% vs. 70.90%, $p=0.25$) or 5-year BCSS rate (74.64% vs. 77.31%, $p=0.25$), but HR-negative patients had significant improvements in both the OS rate (64.58% vs. 71.34%, $p=0.0051$) and BCSS rate (73.14% vs. 78.07%, $p=0.035$) (Fig. 1).

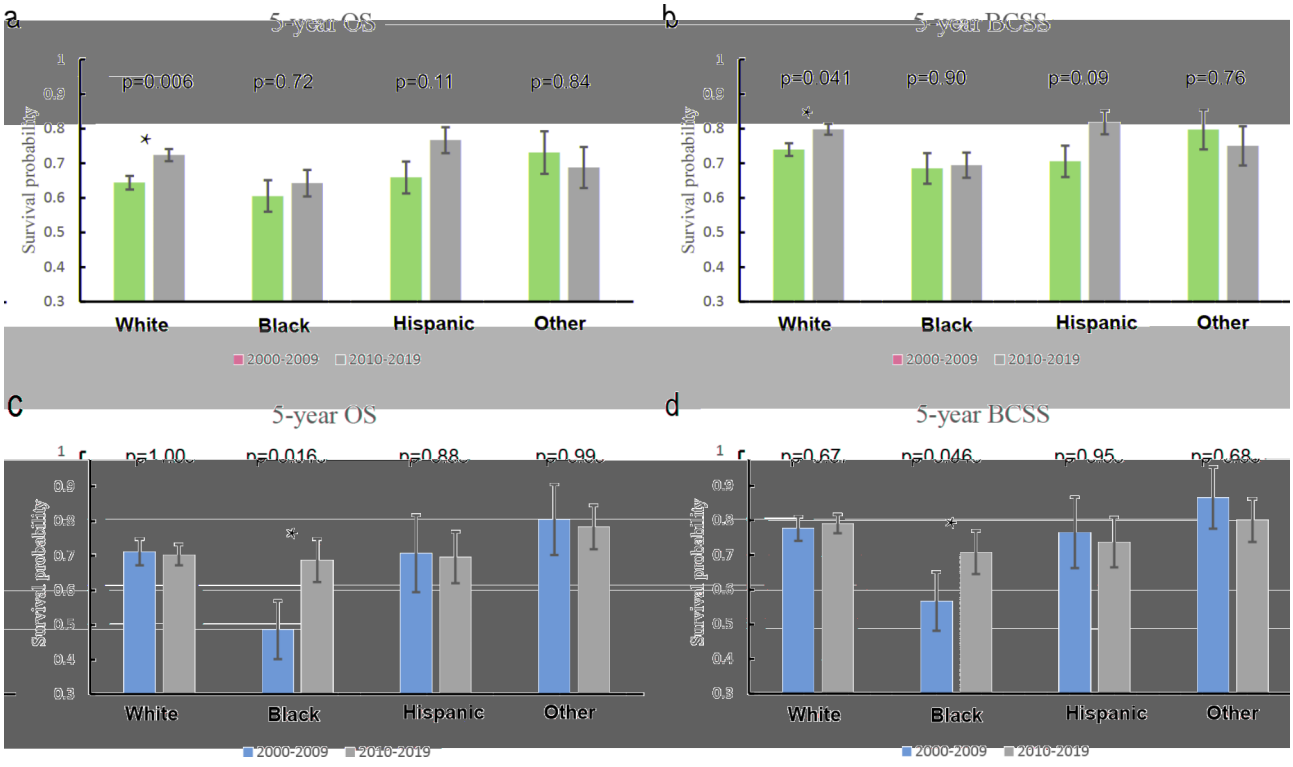

Fig. 2 Survival probability of metaplastic breast cancer patients by race over time. (**a**, **b**) Five-year overall survival and breast cancer-specific survival of different races among the hormone receptor-negative patients; (**c**, **d**) five-year overall survival and breast cancer-specific survival of different races among the hormone receptor-positive patients. P values were determined via the univariate log-rank test

Multivariate analysis of survival data

This study obtained adjusted HRs for OS and BCSS by using multivariable Cox proportional hazards models. For HR-negative patients, the hazards were significantly lower in 2010–2019 compared to 2000–2009 in terms of both OS (adjusted HR=0.83, 95% CI: 0.71–0.97, p=0.021) and BCSS (adjusted HR=0.83, 95% CI: 0.69–1.00, p=0.045), indicating better survival outcomes in the more recent period. In contrast, for HR-positive patients, OS and BCSS did not show any significant improvements in 2010–2019 compared to 2000–2009. The variables significantly correlated with OS and BCSS in HR-negative MpBC patients were age, White (Black as reference), T stage (T0 and T1 as references), lymph node status (negative as reference), surgery type (BCS as reference) and radiotherapy (Table 2, all p<0.05). The associated variables significantly associated with the OS and BCSS of HR-positive MpBC patients were T stage (T0&T1 as reference) and lymph node status (negative as reference). For HR-positive patients, those aged ≥ 50 years only correlated with worse OS. Receiving chemotherapy was a protective factor for the OS of MpBC patients with any HR status (Table 2).

Trends in cancer characteristics

A multivariate logistic regression model was constructed to determine whether survival trends could be attributed to changes in demographic and pathological characteristics (Table 3). Compared with those from 2000 to 2009, the ORs for HR- negative patients who were White were significantly lower from 2010 to 2019 (OR=0.78, 95% CI: 0.65–0.94; p=0.009). There was a greater likelihood of HR-negative patients having negative nodes (OR=1.33, 95% CI: 1.10–1.62, p=0.004) and a lower OR of positive nodes (OR=0.72, 95% CI: 0.58–0.90, p=0.003) in the latter time period. In the same subgroup, a significantly lower likelihood of patients with T2 stage disease was noted from 2010 to 2019 (OR=0.81, 95% CI: 0.68–0.96, p=0.016). A lower OR was found in patients with stage T0 & T1 disease (OR=0.63, 95% CI: 0.44–0.92, p=0.015) than in those with stage T0 & T1 disease (OR=0.63, 95% CI=0.44–0.92, p=0.015) in the HR-positive subgroup.

Survival trends by race/ethnicity

Subgroup analysis indicated that, regardless of the HR status, there were no significant differences in OS or BCSS among different races (all p>0.05) (Supplementary Fig. 5). A significant improvement was observed in the 5-year OS rate (64.39% vs. 72.39%, p=0.0063) and 5-year BCSS rate (73.94% vs. 79.83%, p=0.041) among

Table 1 Comparison of the baseline characteristics of metaplastic breast cancer between the two groups at different time points

Time Period	2000–2009	2010–2019	
Variables	***N*=1079**	***N*=1997**	***P*[a]**
Age			0.130
<50	267(24.7%)	446(22.3%)	
≥50	812(75.3%)	1551(77.7%)	
Race/Ethnicity			**0.014**
Black	149(13.8%)	313(15.7%)	
White	737(68.3%)	1256(62.9%)	
Hispanic	124(11.5%)	252(12.6%)	
Other	69(6.4%)	176(8.8%)	
Marital Status			0.415
Married	563(52.2%)	1018(51.0%)	
Unmarried	483(44.8%)	900(45.1%)	
Unknown	33(3.1%)	79(4.0%)	
Median Household Income			0.106
<$50,000	134(12.4%)	299(15.0%)	
$50,000–75,000	622(57.6%)	1145(57.3%)	
>$75,000	323(29.9%)	553(27.7%)	
Grade			0.347
I	43(4.0%)	73(3.7%)	
II	118(10.9%)	244(12.2%)	
III&IV	779(72.2%)	1389(69.6%)	
Unknown	139(12.9%)	291(14.6%)	
T Stage			0.556
T0&T1	271(25.1%)	517 (25.9%)	
T2	566(52.5%)	996(49.9%)	
T3	168(15.6%)	333(16.7%)	
T4	74(6.9%)	151(7.6%)	
HR Status			**<0.001**
HR-positive	210(19.5%)	546(27.3%)	
HR-negative	869(80.5%)	1451(72.7%)	
Lymph Node Status			**0.012**
Positive	256(23.7%)	383(19.2%)	
Negative	747(69.2%)	1468(73.5%)	
Unknown	76(7.0%)	146(7.3%)	
SurgeryType			0.417
BCS	458(42.4%)	878(44.0%)	
Mastectomy	621(57.6%)	1119(56.0%)	
Radiotherapy			**0.002**
No/Unknown	592(54.9%)	981(49.1%)	
Yes	487(45.1%)	1016(50.9%)	
Chemotherapy			**<0.001**
No/Unknown	442(41.0%)	641(32.1%)	
Yes	637(59.0%)	1356(67.9%)	
HER2 Status			NA[b]
Positive	0(0.0%)	111(5.6%)	
Negative	0(0.0%)	1830(91.6%)	
Borderline/Unknown	1079(100.0%)	56(2.8%)	

Abbreviations: HR, hormone receptor; BCS, breast conserving surgery; HER2, human epidermal growth factor 2. [a] P value from Pearson's chi-square test of independence. [b] HER2 status is not comparable, as it was not registered prior to 2010

White patients in the HR-negative subgroup. In the HR-positive subgroup, there was a significant increase in the OS rate (48.57% vs. 68.63%, $p=0.016$) and 5-year BCSS rate (56.60% vs. 70.75%, $p=0.046$) among Black patients (Fig. 2).

Trends in treatment

The OR of treatment was obtained by using a multivariable logistic regression model (Table 4). There was no significant difference in the number of HR-negative patients who had undergone mastectomy or radiotherapy, but the number of patients who received chemotherapy increased significantly from 2010 to 2019 (OR=1.76, 95% CI: 1.44–2.15, $p<0.001$). Subgroup analysis suggested that White patients (OR=2.01, 95% CI: 1.57–2.58, $p<0.001$) in the HR-negative population received more chemotherapy. Additionally, HR-positive patients had a greater OR for radiotherapy (OR=1.76, 95% CI: 1.17–2.65, $p=0.007$) but not for mastectomy or chemotherapy. Subgroup analysis suggested that Black patients (OR=3.83, 95% CI: 1.20–13.62, $p=0.029$) received more radiotherapy in the HR-positive subgroup.

Discussion

This study evaluated the survival trends of MpBC patients with different HR statuses who were registered in the SEER database from 2000 to 2019. This is the only series to evaluate survival outcomes for MpBC by HR status. This study revealed that the survival of HR-negative MpBC patients has improved significantly over the past two decades, whereas such improvement was not observed for HR-positive patients. Additionally, there was an increasing trend in HR-positive MpBC patients over time. Previous research has noted a similar trend for nonspecific types of breast cancer in the United States [10]. This finding may reflect the changes in risk factors associated with the HR status of MpBC, such as obesity and fertility patterns [11, 12]. Additionally, it could reflect the evolving definition of HR-positive disease. The 2010 ASCO/CAP guidelines introduced adjustments to the thresholds for ER and PR positivity, reducing the positive rate of tumour nuclei in samples from 10–1% [13] and consequently increasing the proportion of patients classified as HR-positive. There has been a significant improvement in the survival of White patients in the HR-negative subgroup over the past decade. Compared with Black patients, White patients with HR-negative MpBC have significantly better outcomes. Racial and ethnic differences in socioeconomic status, insurance and education status may affect the effectiveness of treatment of breast cancer [14, 15]. Furthermore, White patients feature superior treatment quality, earlier initiation of treatment, greater adherence to treatment and better health outcomes than Black patients do [16–19]. This may

Table 2 Multivariable Cox regression for breast cancer-specific mortality and overall mortality associated with different hormone receptor statuses (only statistically significant results are shown in bold)

	Hormone Receptor-Negative				Hormone Receptor-Positive			
	Overall Survival		Breast Cancer-Specific Survival		Overall Survival		Breast Cancer-Specific Survival	
Variable[a]	**Adjusted HRs (95% CI)**	***P***	**Adjusted HRs (95% CI)**	***P***	**Adjusted HRs (95% CI)**	***P***	**Adjusted HRs (95% CI)**	***P***
Time Period								
2000–2009	1	Ref	1	Ref	1	Ref	1	Ref
2010–2019	0.83 (0.71–0.97)	**0.021**	0.83 (0.69–1.00)	**0.045**	0.9 (0.66–1.24)	0.525	0.87 (0.61–1.24)	0.428
Age								
< 50	1	Ref	1	Ref	1	Ref	1	Ref
≥ 50	1.50 (1.21–1.88)	**< 0.001**	1.33 (1.06–1.68)	**0.016**	1.60 (1.05–2.42)	**0.027**	1.52 (0.97–2.37)	0.066
Race/Ethnicity								
Black	1	Ref	1	Ref	1	Ref	1	Ref
White	0.80 (0.65–1.00)	**0.049**	0.76 (0.59–0.97)	**0.027**	0.74 (0.50–1.10)	0.136	0.68 (0.44–1.06)	0.086
Hispanic	0.80 (0.58–1.08)	0.149	0.73 (0.52–1.03)	0.073	0.74 (0.41–1.32)	0.309	0.74 (0.39–1.39)	0.352
Other	0.76 (0.52–1.12)	0.173	0.70 (0.45–1.09)	0.113	0.53 (0.28–1.04)	0.063	0.56 (0.27–1.14)	0.111
T Stage								
T0&T1	1	Ref	1	Ref	1	Ref	1	Ref
T2	1.57 (1.20–2.06)	**0.001**	1.65 (1.18–2.31)	**0.003**	2.47 (1.51–4.02)	**< 0.001**	3.21 (1.70–6.06)	**< 0.001**
T3	3.94 (2.94–5.28)	**< 0.001**	4.83 (3.37–6.90)	**< 0.001**	3.91 (2.22–6.87)	**< 0.001**	5.22 (2.58–10.59)	**< 0.001**
T4	5.51 (3.94–7.70)	**< 0.001**	7.08 (4.78–10.49)	**< 0.001**	7.04 (3.92–12.63)	**< 0.001**	9.72 (4.69–20.14)	**< 0.001**
Node Status								
Negative	1	Ref	1	Ref	1	Ref	1	Ref
Positive	2.00 (1.66–2.41)	**< 0.001**	2.23 (1.82–2.74)	**< 0.001**	2.22 (1.57–3.13)	**< 0.001**	2.27 (1.56–3.32)	**< 0.001**
Unknown	2.07 (1.59–2.68)	**< 0.001**	1.76 (1.25–2.48)	**0.001**	2.57 (1.63–4.05)	**< 0.001**	1.70 (0.95–3.06)	0.076
Surgery Type								
BCS	1	Ref	1	Ref	1	Ref	1	Ref
Mastectomy	1.39 (1.13–1.71)	**0.002**	1.32 (1.04–1.68)	**0.024**	1.31 (0.88–1.94)	0.180	1.27 (0.80–2.00)	0.311
Radiotherapy								
No/Unknown	1	Ref	1	Ref	1	Ref	1	Ref
Yes	0.72 (0.60–0.86)	**< 0.001**	0.70 (0.58–0.86	**0.001**	0.70 (0.48–1.02)	0.062	0.67 (0.44–1.02)	0.059
Chemotherapy								
No/Unknown	1	Ref	1	Ref	1	Ref	1	Ref
Yes	0.63 (0.52–0.75)	**< 0.001**	NA[b]	NA	0.55 (0.38–0.79)	**0.001**	0.70 (0.46–1.06)	0.093

The analysis was adjusted for age, race, marital status, median household income, pathologic grade, T stage, lymph node status, surgery type, and receipt of radiation and chemotherapy

Abbreviations: BCS, breast-conserving surgery; HR, hazard ratio; CI, confidence interval

[a] Univariate regression analysis $p=0.468$, which was not included in the multivariable Cox regression

account for the apparent improvement in White patient's survival. This study also found a significantly increased ratio in patients aged ≥ 50 years in the HR subgroup, possibly as a result of population ageing. Although this study and previous studies have shown that old age is a predictor of a poor outcome for MpBC [9, 20, 21], it is clear that changes in age structure have little effect on the survival trend of MpBC.

This study observed potential racial disparities in the incidence of MpBC across different HR statuses. Compared with White and Asian women, African American women and Hispanic women in the United States present higher incidence rates of HR-negative breast cancer, referring to the patterns observed in nonspecific types of breast cancer [22]. Another study revealed that later age at menarche was not associated with HR-positive breast cancer incidence in African American women [23]. In the last 10 years, the proportion of Whites in the HR-negative subgroup has decreased significantly, whereas the proportions of Black, Hispanic and other races have increased accordingly. Research indicates that the incidence of traditional breast cancer is increasing in all race/ethnic groups, whereas the increasing trend in incidence among Whites is relatively minor [24]. This trend may be attributed to the changes in risk factors associated with MpBC. In recent years, the increase in body mass index (BMI) and fertility rates among Black women in the United States has been more significant than that among White women, both of which are believed to be positively associated with the incidence of breast cancer

Table 3 Trends for age and race derived from each time period for different hormone receptor statuses of metaplastic breast cancer. Analysis adjusted for age, race, marital status, median household income, pathologic grade, T stage, and lymph node status

	Hormone Receptor-Negative					Hormone Receptor-Positive				
	2000–2009		2010–2019			2000–2009		2010–2019		
Variable	**%**	**OR**	**%**	**OR (95% CI)**	***P***	**%**	**OR**	**%**	**OR (95% CI)**	***P***
Age										
≥ 50	75.4	1	79.3	1.25(1.01–1.53)	**0.037**	74.8	1	73.4	1.06(0.71–1.57)	0.759
Race/Ethnicity										
Black	13.1	1	15.6	1.18(0.92–1.51)	0.205	16.7	1	15.8	1.05(0.67–1.67)	0.841
White	68.5	1	64.2	0.78(0.65–0.94)	**0.009**	67.6	1	59.3	0.72(0.51–1.02)	0.066
Hispanic	12.3	1	12.6	1.13(0.87–1.48)	0.359	8.1	1	12.6	1.40(0.80–2.56)	0.251
Other	6.1	1	7.5	1.37(0.97–1.94)	0.076	7.6	1	12.3	1.60(0.91–2.97)	0.116
Node Status[a]										
Positive	22.9	1	17.9	0.72(0.58–0.90)	**0.003**	27.1	1	22.5	0.69(0.47–1.01)	0.056
Negative	70.4	1	75.3	1.33(1.10–1.62)	**0.004**	64.3	1	68.9	1.31(0.92–1.85)	0.128
T Stage										
T0&T1	23.0	1	25.8	1.16(0.94–1.42)	0.167	33.8	1	26.2	0.63(0.44–0.92)	**0.015**
T2	54.4	1	49.2	0.81(0.68–0.96)	**0.016**	44.3	1	51.6	1.35(0.98–1.87)	0.069
T3	15.9	1	17.3	1.11(0.88–1.40)	0.379	14.3	1	15.0	1.10(0.70–1.78)	0.686
T4	6.7	1	7.7	1.22(0.87–1.72)	0.258	7.6	1	7.1	1.08(0.58–2.10)	0.810

Abbreviations: OR odds ratio, CI confidence interval

[a]Analysis not shown for an unknown race. [b]Analysis not shown for unknown node status

Table 4 Trends for treatment derived from each time period for different hormone receptor statuses of metaplastic breast cancer. The analysis was adjusted for age, race, marital status, median household income, pathologic grade, T stage, lymph node status, surgery type, and receipt of radiation and chemotherapy

	Hormone Receptor-Negative			Hormone Receptor-Positive		
	2000–2009	2010–2019		2000–2009	2010–2019	
Variable	**OR**	**OR (95% CI)**	***P***	**OR**	**OR (95% CI)**	***P***
Mastectomy						
All patients	1	1.02(0.82–1.26)	0.873	1	0.96(0.62–1.48)	0.842
Black	1	1.17(0.67–2.03)	0.588	1	0.38(0.11–1.26)	0.122
White	1	1.04(0.79–1.36)	0.799	1	1.01(0.59–1.74)	0.969
Radiotherapy						
All patients	1	1.11(0.91–1.35)	0.298	1	1.76(1.17–2.65)	**0.007**
Black	1	1.53(0.94–2.50)	0.091	1	3.83(1.20–13.62)	**0.029**
White	1	1.13(0.88–1.46)	0.327	1	1.55(0.93–2.59)	0.093
Chemotherapy						
All patients	1	1.76(1.44–2.15)	**< 0.001**	1	1.35(0.91–2.01)	0.135
Black	1	1.24(0.71–2.17)	0.443	1	2.08(0.75–5.85)	0.156
White	1	2.01(1.57–2.58)	**< 0.001**	1	1.45(0.89–2.35)	0.135

Abbreviations: OR odds ratio, CI confidence interval

[25]. Increased utilization of screening may also be a contributing factor. Studies have shown that, compared with Whites, Black, Hispanic, and Native Americans have narrowed the gap in mammography utilization rates [26, 27]. The incidence of breast cancer is positively correlated with socioeconomic status [28], and further exploration is required to investigate whether similar associations exist among patients with MpBC.

The improved survival of patients with MpBC may be attributed to early diagnosis. MpBC typically presents with less nodal involvement. Like the nonspecific types of breast cancer, lymph node negative MpBC has a better prognosis [29]. This study confirmed that lymph node status is associated with prognosis. Moreover, the proportion of HR-negative patients with negative lymph nodes increased significantly in the latter period, while there was no similar trend in HR-positive patients, which indicates that more HR-negative patients were diagnosed before lymph node metastasis, reflecting a stage shift towards earlier diagnosis. In addition, it is reasonable to investigate whether the pattern of lymph node metastasis varies according to HR status. As mentioned above, the use of mammography for the diagnosis of breast cancer has increased in multiple ethnicities, which

may contribute to early diagnosis. However, research shows that MpBC lacks characteristic imaging features on mammography [30]. Owing to the scarcity of cases, there are few studies on imaging diagnosis of MpBC. The results reported here will serve as the basis for future research addressing this issue.

Local treatment has a limited effect on the survival improvement of MpBC, and this study did not find any trend in the surgical approach over time for MpBC. Advances in the surgical treatment of breast cancer over the past few decades have focused on improving cosmetic outcomes and minimizing functional sequelae. MpBC patients, because of their larger tumour sizes, usually undergo mastectomy more often than those with BCS, and the rate of BCS is much lower in MpBC than in IDC [3, 4, 31, 32]. This study revealed that mastectomy is associated with poorer survival in HR-negative patients than BCS is. One possibility is that BCS plus adjuvant radiotherapy may reduce local recurrence and improve survival in patients with MpBC. In addition, MpBC patients who underwent BCS were generally at an earlier stage than those who underwent mastectomy.

Current progress in radiotherapy for breast cancer has focused mainly on hypofractionation [33]. For MpBC, the effectiveness of radiotherapy has yet to be determined, and there is an absence of data examining the relationship between the boost dose and efficacy for MpBC. Studies have shown that radiotherapy is associated with improved OS and BCSS in patients with MpBC [34, 35]. However, Rakha et al. reported that postoperative adjuvant radiotherapy was not associated with survival [36], and others reported that low-risk MpBC patients cannot benefit from radiotherapy [37]. This study confirmed that radiotherapy contributed to better survival in only HR-negative MpBC patients, suggesting that HR status may affect the effect of radiotherapy on MpBC. Similarly, Hu reported that radiotherapy is correlated with improved survival in triple-negative but not HR-positive MpBC patients [38]. The paradox is that an increase in radiotherapy utilization was found in HR-positive patients during the study period, but survival did not improve, possibly because physicians may recognize that HR-positive MpBC treatment is less effective and add radiation therapy. This study also revealed significant survival improvements and increased use of radiotherapy in HR-positive Black patients, and whether there is an association needs to be further explored.

Chemotherapy is a routine treatment for patients with MpBC, but some studies have suggested that chemotherapy has a limited effect on MpBC [39–41]. Wang et al. noted that only HR-positive MpBC patients at high risk could benefit from chemotherapy [42]. Like other studies [32, 34], the findings of this study also suggest that, regardless of HR status in MpBC patients, chemotherapy could improve OS. This study revealed an increase in the utilization of chemotherapy in HR-negative MpBC patients during the latter period, and the use of chemotherapy increased in Whites in this subgroup, which may account for the improved survival of these patients. As most HER2 receptors in MpBC are negative, anti-HER2 therapy cannot be considered a suitable treatment option.

Research confirms that genetic alterations in the phosphatidylinositol-3 kinase signalling pathway (PI3K) [43] or epithelial-to-mesenchymal transition [44] may lead to the aggressiveness and poor prognosis of MpBC. In a phase one clinical trial involving 52 patients with advanced metaplastic TNBC a combination of an mTOR inhibitor, bevacizumab, and liposomal doxorubicin achieved an objective response rate (ORR) of 21% [45]. In addition, a clinical trial in which the PI3K inhibitor buparlisib combined with paclitaxel was used for the treatment of MpBC achieved a sustained response during treatment and a 42-month OS [46]. Adams et al. [47] reported that the immunotherapy drugs ipilimumab and nivolumab resulted in a response 2 to 3 years later in the treatment of advanced MpBC. Given the poor outcome of MpBC, there is an urgent need to identify better systemic treatments for potential molecular targets.

In contrast to the trend of improved survival in HR-negative MpBC patients, five-year survival in HR-positive patients has remained stagnant over the last decade. Previous studies reported that there were no differences in the prognosis of HR-positive patients who received antioestrogen therapy compared with those who did not [48, 49]. Owing to missing data on endocrine therapy, this study was unable to analyse whether HR-positive patients could benefit from endocrine therapy. Patients with distant metastases were excluded from this study, and owing to the nature of fewer lymph node metastases, fewer patients are likely to benefit from novel drugs such as CDK4/6 inhibitors, which tend to have strict indications for lymph node metastases. The role of antihormonal therapy in HR-positive MpBC may require further investigation.

There are, however, some limitations in this study. First, retrospective analyses can be subject to selection bias, and the findings of this study must be interpreted in the context of the data, as with any retrospective analysis. This study is unable to provide an accurate count of patients with unknown chemotherapy and radiotherapy status, as the record in the SEER database is classified as no/unknown without distinguishing between them. In addition, the specific chemotherapy regimen remains unknown because detailed information on the treatment is missing from the SEER database. HER2 was not available as a key variable in breast cancer treatment until 2010. Other information, such as family history and

complications, was not recorded. There was a change in the threshold for defining HR negativity from 10 to 1%. The SEER database does not provide rates of hormone receptor staining. Therefore, an analysis of MpBC with low HR expression (1-10%) could not be conducted separately. Therefore, when interpreting the results of this study, it would be more appropriate to consider HR negativity as less than 10% of positively stained cells.

Conclusion

This study identified significantly improved survival in HR-negative MpBC patients over the last 20 years, but the trend was not significant in HR-positive patients. The reason might be attributed to early diagnosis and the increased use of chemotherapy. In addition, medical advances are likely to affect temporal changes in long-term survival in MpBC patients, but the exact extent of their impact is difficult to measure. Regardless of genetic factors, differences in risk factors or treatment may account for the racial disparity in MpBC across HR statuses. Since MpBC is composed of multiple pathologies and different pathologies present different clinical characteristics, unifying treatment modalities is difficult. Currently, little is known about the mechanisms of MpBC occurrence and metastasis, and there are no specific guidelines for clinical treatment. Further studies are needed to define the biological characteristics of MpBC, and more clinical trials and precise guidelines regarding the management of adjuvant or neoadjuvant therapies are needed.

Abbreviations

MpBC	Metaplastic breast carcinoma
HR	Hormone receptor
IDC	Invasive ductal carcinoma
WHO	World Health Organization
BCS	Breast conserving surgery
OR	Odds ratio
IDC	Invasive ductal carcinoma
SEER	Surveillance, Epidemiology, and End Results
HRs	Hazard ratios
ER	Estrogen receptor
PR	Progesterone receptor
Her-2	Human-epidermal growth factor receptor 2
TNBC	Triple-negative breast cancer
OS	Overall survival
BCSS	Breast cancer-specific survival

Supplementary Information

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Supplementary Material 1

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Author contributions

YY was responsible for the concept and design of the study. All authors contributed to the acquisition, analysis, and interpretation of the data. The draft was produced by MZ and BF. The statistical analysis was conducted by WZ, CK, XS and GF, while YY provided administrative, technical support. All authors have read and approved the final manuscript.

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Data availability

The datasets analyzed in the present study can be obtained from the SEER program online website (https:// seer. cancer.gov). The datasets are also available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was exempt from the approval processes of the Institutional Review Boards because the SEER database patient information is de-identified. The need for written informed consent was waived for The SEER Dataset was a public-use dataset.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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