The Breast 58 (2021) 10–17

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Survival outcomes after breast-conserving therapy compared with mastectomy for patients with early-stage metaplastic breast cancer: a population-based study of 2412 patients

Junsheng Zhang [a, b, 1], Ciqiu Yang [a, 1], Chuqian Lei [c, 1], Yi Zhang [a], Fei Ji [a], Hongfei Gao [a], Mei Yang [a], Liulu Zhang [a], Jieqing Li [a], Teng Zhu [a], Weiping Li [a, d], Xiaosheng Zhuang [a, b], Kun Wang [a, b, *]

[a] Department of Breast Cancer, Cancer Center, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, 510080, China
[b] Shantou University Medical College, Shantou, 515041, China
[c] Department of Breast Surgery, The Eighth Affiliated Hospital, Sun Yat-sen University, Shenzhen, 518000, China
[d] The Second School of Clinical Medicine, Southern Medical University, Guangzhou, 510515, China

ARTICLE INFO

Article history:
Received 4 January 2021
Received in revised form
18 March 2021
Accepted 29 March 2021
Available online 1 April 2021

Keywords:
Breast neoplasms
Carcinoma
Breast-conserving surgery
Mastectomy
Survival

ABSTRACT

Background: Previous studies revealed that patients with early-stage metaplastic breast cancer (MBC) underwent mastectomy more often than breast-conserving therapy (BCT) mainly due to the larger tumor size. This study was performed to compare the survival outcomes following BCT versus mastectomy for patients with early-stage MBC.

Methods: Surveillance, Epidemiology, and End Results (SEER) database was used to identify women diagnosed with early-stage MBC (T1-3N0-3M0) between 2001 and 2016, who were treated with either BCT or mastectomy. We assessed overall survival (OS) and breast cancer-specific survival (BCSS) using the Kaplan-Meier method and hazard ratios using Cox proportional hazards models.

Results: A total of 2412 MBC patients were identified, 881 (36.5%) of whom underwent BCT and 1531(63.5%) underwent mastectomy. The median follow-up time was 73 months. Most of patients had older age (≥50 years old), larger tumor size, higher American Joint Committee on Cancer (AJCC) stage and hormone receptor negativity. After adjustment for confounding variables, patients who underwent BCT had significantly improved OS (5-year OS: 84.3% vs 62.5%; 10-year OS: 73.0% vs 52.1%; adjusted HR = 0.76, 95%CI: 0.59–0.97, p = 0.028) and BCSS (5-year BCSS: 89.1% vs 70.8%; 10-year BCSS: 83.9% vs 67.5%; adjusted HR = 0.72, 95%CI: 0.53–0.96, p = 0.026) than those who underwent mastectomy, and this improvement remained significant for all T and N stages of MBC except for N2-3 stage.

Conclusion: BCT conferred improved OS and BCSS compared with mastectomy for patients with early-stage MBC, and the improvement persisted in almost all of the subgroups of different T and N stages.

1. Introduction

Surgical therapy of the primary breast cancer, including breast-conserving therapy (BCT, lumpectomy with whole breast radiation) and mastectomy, is currently thought to be one of the most important treatments for early-stage breast cancer. The relationship between the surgical options and survival outcomes for early-stage breast cancer patients has been explored for decades. NSABP B06 Trial and Milan Trial demonstrated BCT was equivalent to mastectomy with respect to survival [1,2]; subsequently, several randomized clinical trials (RCTs) also reported the similar results [3–5]. However, all of these studies were launched approximately 30 years ago. In the past decades, systemic treatment and locoregional radiation of breast cancer have been notably improved, which significantly contributed to better survival for breast cancer patients, consequently influencing doctors' choice of surgical

* Corresponding author. Department of Breast Cancer, Cancer Center, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences. No. 123 Huifu West Road, Guangzhou, 510080, China.
E-mail address: gzwangkun@126.com (K. Wang).
[1] Junsheng Zhang, Ciqiu Yang and Chuqian Lei contributed equally to this study.

https://doi.org/10.1016/j.breast.2021.03.010

approaches on local treatment. Recently, a series of large population-based studies were conducted to investigate the impact of surgical treatment (BCT or mastectomy) on survival outcomes and found BCT had better survival than mastectomy for patients with early-stage breast cancer [6–12].

Metaplastic breast cancer (MBC), accounting for 0.2–5.0% of all breast cancer, is clinically aggressive and associated with poor prognosis [13–19]. Compared to invasive ductal carcinoma (IDC), the most common subtype of breast cancer, MBC typically presents with larger tumor size, higher American Joint Committee on Cancer (AJCC) stage, higher tumor grade as well as hormone receptor negativity and occurs in female older than 50 years old, which are related to dismal outcomes on survival [19–21]. Since the majority of MBC were triple-negative, hormonal therapy and targeted therapy were usually ineffective for patients with MBC [16,18,22]. Furthermore, MBC was more resistant to chemotherapy and had worse prognosis than triple negative breast cancer (TNBC) [17,19,23–25]. As MBC is typically aggressive and resistant to systemic therapy, surgery treatment of the primary site is closely associated with survival outcomes. Currently, MBC is treated with the principles that are applied to more common breast cancers. For surgical treatment of the primary breast cancer, the National Comprehensive Cancer Network (NCCN) guidelines recommend that mastectomy is equivalent to BCT with respect to survival. Several retrospective studies revealed that patients with MBC were treated more often with mastectomy mainly due to the larger tumor size [16,18,19]. However, one of the studies mentioned that breast-conserving surgery led to superior 3-year overall survival compared with mastectomy regardless of stage at presentation, but did not clarify the result or conduct the stratified analysis [18]. Therefore, the relationship between surgical approaches and survival outcomes for MBC patients has yet to be elucidated.

The present study was performed to investigate the impact of surgical approaches (BCT or mastectomy) on the survival outcomes of early-stage MBC patients using the Surveillance, Epidemiology, and End Results (SEER) database. To eliminate the influence of clinical stage, which was considered one of the most important factors that may influence the choice of primary breast local treatment, our study also conducted subgroup analysis according to AJCC T and N stage.

2. Materials and methods

2.1. Study population

All data was extracted from the Surveillance, Epidemiology, and End Results (SEER) database that updated in November 2016. The SEER database, including 18 tumor registries and representing approximately 28% of the population across the United States, contained detailed information about demographics, tumor characteristics, nodal staging, surgery type, survival months and vital status [18,19]. Since the World Health Organization (WHO) did not recognize MBC as a distinct pathologic subtype until 2000 [19,26], we identified 4509 women diagnosed with MBC (International Classification of Diseases for Oncology, third edition (ICD-O-3) morphology code 8052, 8070, 8071, 8072, 8074, 8560, 8571, 8572, 8575, and 8980) [18] from January 2001 to November 2016, and only those with early-stage breast cancer (T1-3N0-3M0) were selected according to the 6th edition of the AJCC system for cases between 2001 and 2009, and the 7th edition for cases between 2010 and 2016. Patients who had bilateral breast cancer, whose breast cancer was not first primary tumor, who did not undergo breast-conserving therapy or mastectomy and who did not receive radiation along with breast conserving surgery were excluded. The entire cohort was further divided into two groups according to their surgical approach: breast-conserving therapy (BCT) and mastectomy. Finally, 2412 cases were included in our study (Fig. 1).

2.2. Statistical analysis

Pearson's chi-square test was used to compare the patients' characteristics between BCT and mastectomy group. Survival outcomes, including overall survival (OS) and breast cancer-specific survival (BCSS), were examined using the Kaplan-Meier method and compared between the two groups using Log-rank tests. Furthermore, the survival outcomes between BCT and mastectomy group were also analyzed in subgroups according to AJCC T and N stage. The Cox proportional hazard model was used to calculate the hazard ratios (HRs) with 95% confidence intervals (CIs) for both OS and BCSS of the two groups. All tests were two-sided and a P value < 0.05 was applied to indicate statistical significance. All analyses were performed using Statistical Product and Service Solutions (SPSS) software (version 26.0).

3. Results

3.1. Patient characteristics

2412 patients with early-stage MBC (T1-3N0-3M0) were analyzed in our study, among which 881(36.5%) underwent BCT and 1531(63.5%) underwent mastectomy. The median follow-up time was 73 months. Patients' baseline characteristics are showed in Table 1, including patient demographics, tumor characteristics, age of diagnosis, surgery approach, radiation, and chemotherapy. Most patients were White people [27] (78.1% in mastectomy group vs 78.7% in BCT group) and older than or equal to 50 years old (76.3% in mastectomy group vs 78.7% in BCT group), had poorly differentiated or undifferentiated tumor (71.1% in mastectomy group vs 67.7% in BCT group), were in AJCC stage II (72.4% in mastectomy group vs 57.5% in BCT group) and hormone receptor-negative (72.4% in mastectomy group vs 71.2% in BCT group). The mastectomy group had a higher percentage of larger tumor size (>2 cm) than BCT group (83.6% vs 57.0%, $p < 0.001$).

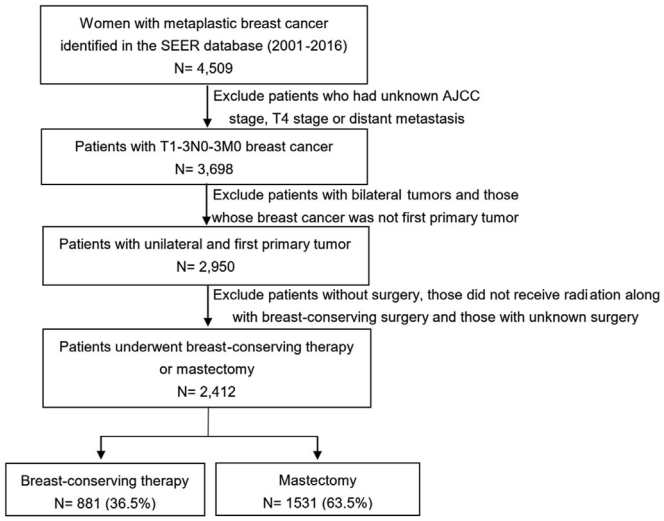

Fig. 1. Flow diagram for creation of the study cohort. Abbreviations: SEER, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer.

Table 1
Comparison of baseline characteristics of early-stage MBC between BCT and mastectomy group.

Characteristics	Patients, No. (%)		P value
	Mastectomy N = 1531(63.5)	BCT N = 881(36.5)	
Race			0.074
White	1195(78.1)	693(78.7)	
Black	218(14.2)	140(15.9)	
Others/Unknown	118(7.7)	48(5.4)	
Age(years)			0.182
18-49	363(23.7)	188(21.3)	
≥50	1168(76.3)	693(78.7)	
Marital status			0.042
Married	786(51.3)	493(56.0)	
Unmarried	690(45.1)	351(39.8)	
Unknown	55(3.6)	37(4.2)	
Grade			0.026
Well differentiated	62(4.0)	53(6.0)	
Moderately differentiated	204(13.3)	125(14.2)	
Poorly differentiated	1016(66.4)	572(64.9)	
Undifferentiated/Anaplastic	73(4.8)	24(2.7)	
Unknown	176(11.5)	107(12.1)	
AJCC stage			<0.001
I	211(13.8)	352(40.0)	
II	1108(72.4)	507(57.5)	
III	212(13.8)	22(2.5)	
T stage			<0.001
T1	251(16.4)	379(43.0)	
T2	855(55.8)	449(51.0)	
T3	425(27.8)	53(6.0)	
N stage			<0.001
N0	1139(74.4)	776(88.1)	
N1	269(17.6)	90(10.2)	
N2-3	123(8.0)	15(1.7)	
HR status			0.234
Negative	1109(72.4)	627(71.2)	
Positive	326(21.3)	209(23.7)	
Borderline/Unknown	96(6.3)	45(5.1)	
LN status			<0.001
Negative	1096(71.6)	732(83.1)	
Positive	368(24.0)	99(11.2)	
No examined	67(4.4)	50(5.7)	
Radiation			<0.001
No	1111(72.6)	0(0.0)	
Yes	420(27.4)	881(100.0)	
Chemotherapy			< 0.001
No/Unknown	601(39.3)	272(30.9)	
Yes	930(60.7)	609(69.1)	

Abbreviations: BCT, breast-conserving therapy; AJCC, American Joint Committee on Cancer; HR, Hormone receptor; LN, lymph node.

3.2. Survival outcomes between mastectomy group and BCT group in overall and subgroup analysis

OS and BCSS of patients in the entire cohort and subgroups stratified by AJCC T and N stage were showed in Table 2. Patients who underwent BCT had significantly improved OS (5-year OS: 84.3% vs 62.5%; 10-year OS: 73.0% vs 52.1%; HR = 0.43, 95%CI: 0.37–0.50, p < 0.001) and BCSS (5-year BCSS: 89.1% vs 70.8%; 10-year BCSS: 83.9% vs 67.5%; HR = 0.38, 95%CI: 0.32–0.46, p < 0.001) than those who underwent mastectomy (Fig. 2). The superiority of BCT in survival outcomes remained significant for all T and N stages of MBC except for N2-3 stage (Figs. 3 and 4).

3.3. Impact of various factors on survival outcomes

Univariate analysis showed that older age (≥50 years old), unmarried status, lager tumor size (>2 cm), higher tumor grade (poorly differentiated or undifferentiated) and clinically positive lymph node are associated with lower OS, while both of radiation and chemotherapy contributed to higher OS (Table 3). In addition, patients with unmarried status, lager tumor size (>2 cm), higher tumor grade (poorly differentiated or undifferentiated tumor) or clinically positive lymph node had lower BCSS, but receiving radiation and chemotherapy were protective factors from breast cancer-related death. Furthermore, patients who underwent BCT had better OS and BCSS compared with those who underwent mastectomy (HR = 0.43, 95%CI: 0.36–0.51, p < 0.001; HR = 0.38, 95%CI: 0.31–0.48, p < 0.001; respectively).

In adjusted multivariate analysis, older age (≥50 years old) and unmarried status were independent risk factors for OS (HR = 1.49, 95%CI: 1.21–1.83, p < 0.001; HR = 1.32, 95%CI: 1.13–1.54, p < 0.001; respectively) but not for BCSS (HR = 1.19, 95%CI: 0.95–1.49, p = 0.129; HR = 1.18, 95%CI: 0.98–1.43, p = 0.090; respectively). Tumor size and clinically positive lymph node were independent risk factors for OS and BCSS. Specifically, patients with T2 and T3 stage had higher risk of death from any cause (HR = 1.54, 95%CI: 1.23–1.92, p < 0.001; HR = 3.63, 95%CI: 2.84–4.64, p < 0.001; respectively) compared with those with T1 stage, as well as higher risk of death from breast cancer (HR = 1.95, 95%CI: 1.42–2.67, p < 0.001; HR = 4.96, 95%CI: 3.55–6.93, p < 0.001; respectively); patients with N1 and N2-3 stage had significantly lower OS (HR = 1.48, 95%CI: 1.21–1.81, p < 0.001; HR = 2.93, 95%CI: 2.30–3.74, p < 0.001; respectively) and BCSS (HR = 1.73, 95%CI: 1.37–2.19, p < 0.001; HR = 3.01, 95%CI: 2.28–3.98, p < 0.001; respectively) compared with those with N0 stage. Receiving chemotherapy regimen was a protective factor for both OS and BCSS (HR = 0.48, 95%CI: 0.40–0.57, p < 0.001; HR = 0.69, 95%CI: 0.56–0.85, p < 0.001; respectively). Concerning the surgical approaches, BCT was favorable to OS and BCSS compared with mastectomy (HR = 0.76, 95%CI: 0.59–0.97, p = 0.028; HR = 0.72, 95%CI: 0.53–0.96, p = 0.026; respectively).

Table 2
OS and BCSS stratified by T and N stage between BCT and mastectomy group.

Stage	All patients	Mastectomy group	BCT group	OS		BCSS	
				HR (95%CI)	P value	HR (95%CI)	P value
Overall	2412	1531	881	0.43(0.37–0.50)	<0.001	0.38(0.32–0.46)	<0.001
T stage							
T1	630	251	379	0.64(0.44–0.94)	0.019	0.50(0.28–0.88)	0.012
T2	1304	855	449	0.59(0.48–0.73)	<0.001	0.69(0.53–0.91)	0.012
T3	478	425	53	0.35(0.25–0.50)	<0.001	0.27(0.18–0.41)	<0.001
N stage							
N0	1915	1139	776	0.48(0.40–0.57)	<0.001	0.45(0.36–0.57)	<0.001
N1	359	269	90	0.36(0.25–0.53)	<0.001	0.31(0.20–0.48)	<0.001
N2-3	138	123	15	0.81(0.42–1.59)	0.569	0.89(0.42–1.87)	0.760

Abbreviations: OS, overall survival; BCSS, breast cancer-specific survival; BCT, breast-conserving therapy; HR, hazard ratios; CI, confidential interval.

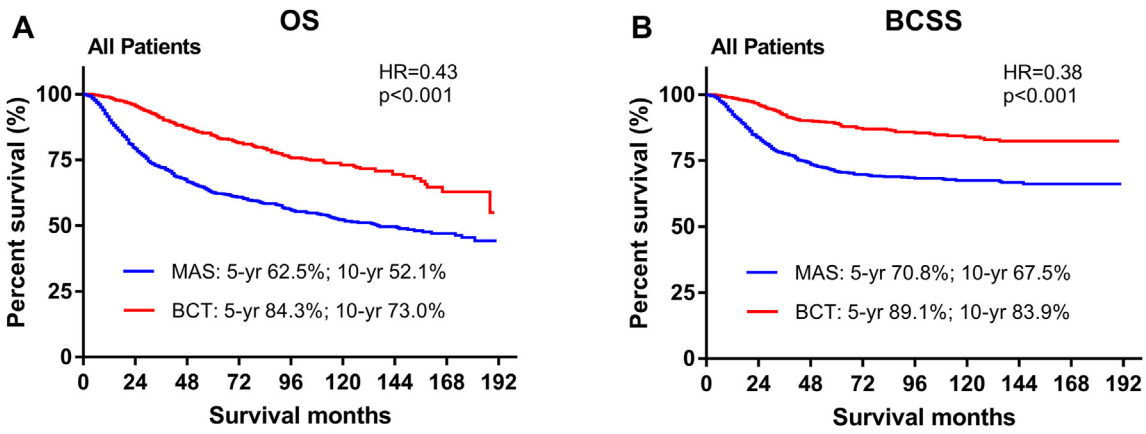

Fig. 2. Kaplan-Meier survival curves of all patients. A. OS between mastectomy and BCT group in the entire cohort; B. BCSS between mastectomy and BCT group in the entire cohort. Abbreviations: OS, overall survival; BCSS, breast cancer-specific survival; MAS, mastectomy; BCT, breast-conserving therapy; HR, hazard ratios.

4. Discussion

Our study investigated the survival outcomes of patients with MBC treated with BCT or mastectomy in a population of 2412 women from the Surveillance, Epidemiology, and End Results (SEER) database, which contained follow-up information from 18 cancer registries with more than 3 million, covering about 28% of the U.S. people. It revealed that BCT had improved 5-year and 10-year OS and BCSS than mastectomy for patients with early-stage MBC after adjustment for confounding variables. Our study found that BCT is better to mastectomy for patients with early-stage MBC with respect to OS and BCSS.

Metaplastic breast cancer (MBC), a rare histologic subtype which accounts for 0.2–5.0% of all breast cancer diagnoses, is clinically aggressive and related to poor prognosis [13–19]. MBC typically presents with larger tumor size, higher AJCC stage, higher tumor grade, less nodal involvement as well as hormone receptor negativity and occurs in female older than 50 years old [16,19,21]. With these aggressive clinical behaviors, MBC tends to have worse outcomes than IDC and even TNBC; studies reported that the 5-year OS of patients with MBC ranges from 54% to 69% compared with 89% for IDC and 73% for TNBC [20,28,29]. As most of MBC were triple-negative, human epidermal growth factor receptor 2 (HER2) targeted therapy was usually ineffective for patients with MBC as well as hormonal therapy [16,18,22]. Given the increased risk of distant metastasis due to larger tumor size, higher tumor grade and triple-negative propensity, combined with lack of hormonal therapy and targeted therapy as adjuvant treatments, patients with MBC are more often treated with systemic chemotherapy than IDC [16,18,19]. However, several studies implicated MBC had lower response to chemotherapy. Rayson et al. identified 27 patients with MBC at Mayo Clinic between 1976 and 1997, who were treated with 10 different chemotherapy regimens, and found only one partial response [30]. They presumed that systemic therapy was less effective in patients with MBC. More recent studies demonstrated that MBC was more resistant to chemotherapy and had worse prognosis than TNBC [23–25]. The chemotherapy-refractory nature and poor survival outcomes of MBC were correlated to the Epithelial-to-Mesenchymal transition (EMT) and stem cell-like features, which promote tumor invasion, migration and development of distant metastases [31,32]. Since MBC was less responsive to systemic treatment, surgical treatment of primary breast cancer appears to be closely related to the survival of patients with MBC. Several retrospective studies revealed that MBC patients underwent mastectomy more often than breast-conserving surgery mainly due to the larger tumor size [16,18,19]. For example, Christopher et al. [16] revealed that MBC patients were treated with mastectomy more frequently than IDC patients (55.6% vs 38.3%, $p < 0.001$) because of the larger tumor size; however, after adjustment for tumor size, no significant difference was observed in the percentages of mastectomy between the two cohorts. Similarly, two population-based studies using the SEER database also reported patients with MBC were treated with mastectomy more frequently [18,19].

Given the rarity of MBC, there are few studies regarding the choice of surgical approaches for patients with MBC. Up to now, MBC is treated with the principles that are developed for more common breast cancers. For surgical treatment of the primary breast cancer, the National Comprehensive Cancer Network (NCCN) guidelines recommend that mastectomy is equivalent to BCT with respect to survival based on several randomized clinical trials [1–5]. However, these trials were launched in 1970s and early 1980s. In the past decades, systemic treatment as well as radiotherapy of breast cancer has been significantly improved, resulting increased survival of breast cancer patients and consequently influencing doctors' choice of surgical approaches for primary breast cancer. Recently, several large population-based studies from various countries suggested BCT had superior survival outcomes compared with mastectomy for patients with early-stage breast cancer [7–12]. Marissa et al. [12] conducted an observational study in which 37,207 women diagnosed with primary early-stage breast cancer from Netherlands were included, and reported that BCT conferred improved 10-year OS compared with mastectomy after stratified analysis for disease stage and adjustment for confounding variables. A study from Canada [10], which included 14,939 patients with stage I-III breast cancer, demonstrated that the patients treated with BCT achieved better OS and BCSS than those with mastectomy, firstly providing the knowledge that BCT conferred survival advantage specifically in stage III patients. Similarly, two other studies from Netherlands [9,11] included patients with T1-2N2 stage breast cancer, and suggested that BCT may be a better surgical option than mastectomy for breast cancer patients. However, most of the patients included into these studies had IDC, which failed to provide convincing evidence for the choices of surgical approaches in patients with MBC.

To our knowledge, this study is the first to investigate the impact of different surgical approaches (BCT or mastectomy) on OS and BCSS of patients with early-stage MBC and conduct subgroup analysis according to AJCC T and N stage. Consequently, we found BCT had better OS and BCSS than mastectomy in all T and N stages

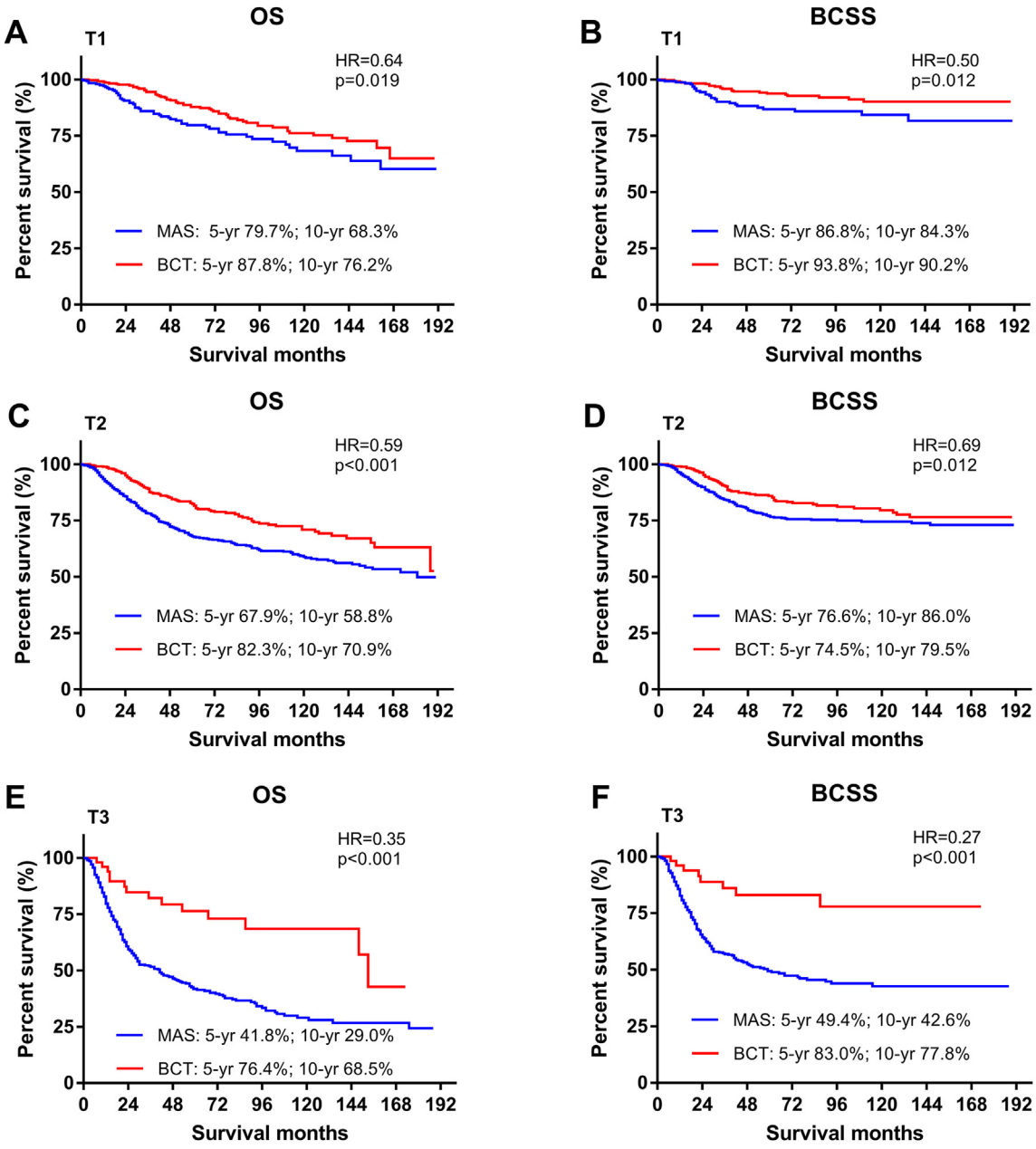

Fig. 3. Kaplan-Meier survival curves of subgroups stratified by T stage. A. OS, T1 stage; B. BCSS, T1 stage; C. OS, T2 stage; D. BCSS, T2 stage; E. OS, T3 stage; F. BCSS, T3 stage. Abbreviations: OS, overall survival; BCSS, breast cancer-specific survival; MAS, mastectomy; BCT, breast-conserving therapy; HR, hazard ratios.

except for N2-3 stage. Rebecca et al. [19] conducted a population-based analysis by identifying 1011 MBC patients and 253,818 IDC patients from SEER database, and revealed that BCT conferred improved disease-specific survival (DSS) compared to mastectomy with or without radiation after adjustment for confounding variables; however, most of the patients in the study had IDC other than MBC. Similarly, another study [18] using the SEER database, including 1516 MBC patients and 220,375 IDC patients from 2010 to 2014, showed that patients treated with breast-conserving surgery had superior 3-year OS compared with those treated with mastectomy regardless of the stage at presentation, but did not report the long-term survival outcomes; meanwhile, whether or not the patients who underwent breast-conserving surgery received radiotherapy was unclear. Both of these two studies did not interpret the result or conduct subgroup analysis to further investigate the relationship between survival outcomes and surgical approaches for patients with MBC. In our study, BCT had significantly improved OS and BCSS compared with mastectomy for patients with MBC after adjustment for various confounding factors, and this improvement persisted in all subgroups of T and N stages except for N2-3 stage. The reason why BCT did not show better survival than mastectomy in patients with N2-3 stage might be attributed to the inadequacy of cases; another explanation was that the surgery approaches may be less likely to influence the survival outcomes of this subset of patients, who suffered local advanced MBC and subsequently had very poor prognosis.

In our study, multivariate analysis demonstrated that older age, unmarried status, larger tumor size (>2 cm) and positive lymph node were associated with decreased overall survival, while hormone receptor positivity, breast-conserving therapy and

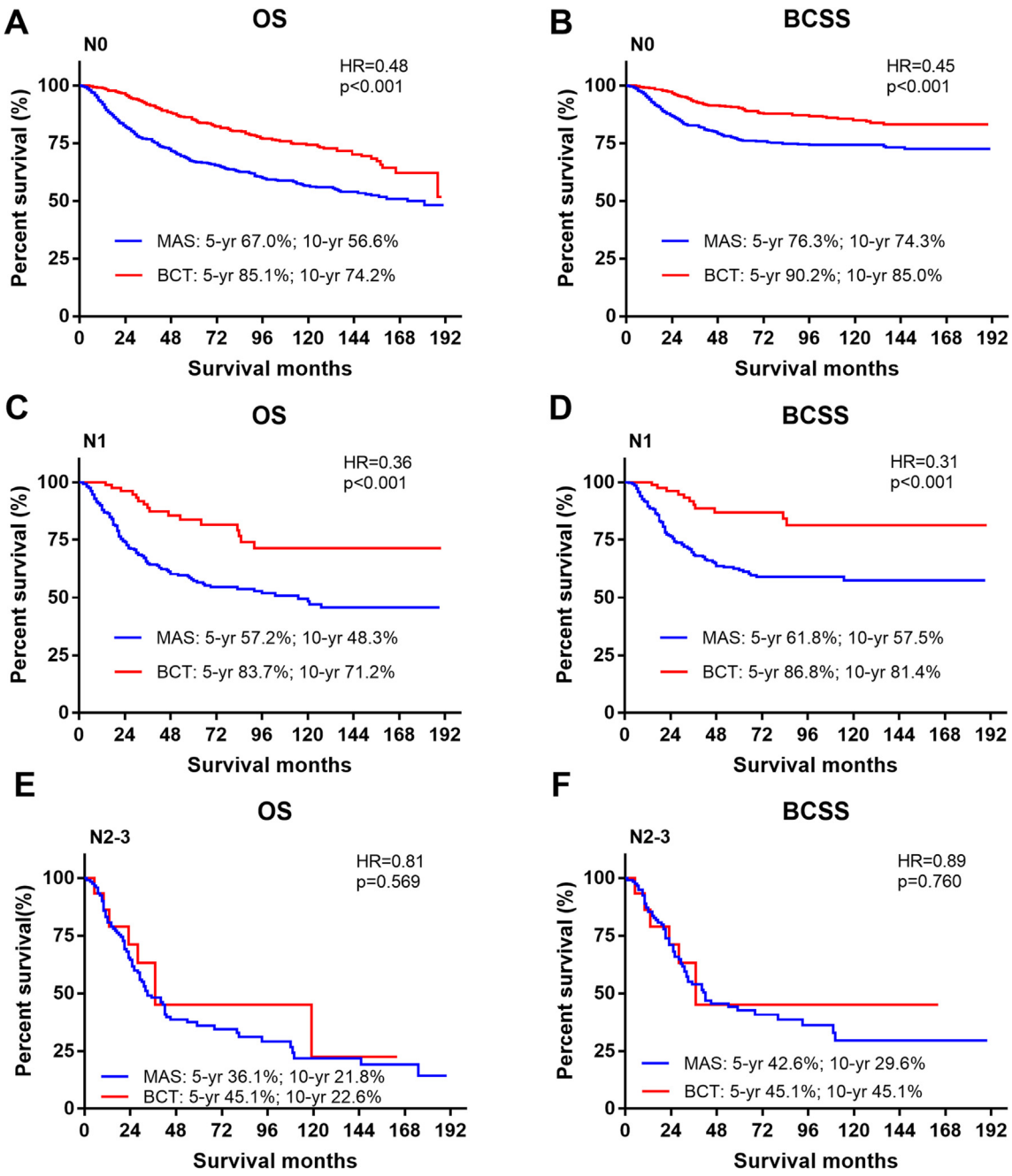

Fig. 4. Kaplan-Meier survival curves of subgroups stratified by N stage. A. OS, N0 stage; B. BCSS, N0 stage; C. OS, N1 stage; D. BCSS, N1 stage; E. OS, N2-3 stage; F. BCSS, N2-3 stage. Abbreviations: OS, overall survival; BCSS, breast cancer-specific survival; MAS, mastectomy; BCT, breast-conserving therapy; HR, hazard ratios.

chemotherapy were related to improved overall survival. This study also showed that breast cancer T and N stage were independent risk factors of BCSS in patients with MBC, and BCT and chemotherapy were associated with superior BCSS compared with mastectomy and non-chemotherapy, respectively. Patients with larger tumor size and positive lymph node were considered to be clinically aggressive and have poorer prognosis, thus having lower overall survival. Eskander et al. [33] found that being married was related to superior OS for patients with breast cancer, which is consistent with our finding. A National Cancer Data Base (NCDB) analysis [34] showed that chemotherapy was an independent predictive factor of overall survival for non-metastatic MBC. He et al. [25] conducted a population-based study from SEER database and confirmed that chemotherapy had survival benefit in the entire MBC cohort; however, no association was detected concerning the subset of triple-negative MBC, which accounted for most of the entire cohort. Because most of MBC patients were triple-negative, the survival benefit of chemotherapy for MBC patients in clinical practice might need further investigation.

A great advantage of our study is the usage of a population-based cancer registry; unlike studies from single institution that had referral bias unavoidably, this study provides a more generalizable clinical practice environment as the SEER database contained information from all levels of healthcare institutions. Investigation of such a rare subtype of breast cancer within a non-selected population is significant for evaluating the choice of surgical

Table 3
Univariate and multivariate analysis of OS and BCSS of patients with early-stage MBC diagnosed between 2001 and 2016.

Characteristics	OS				BCSS			
	Univariate Analysis		Multivariate Analysis*		Univariate Analysis		Multivariate Analysis*	
	HR[a] (95%CI)	P value	HR[a] (95%CI)	P value	HR[a] (95%CI)	P value	HR[a] (95%CI)	P value
Race								
White	Reference	–	Reference	–	Reference	–	Reference	–
Black	1.07(0.87–1.32)	0.50	1.09(0.88–1.34)	0.444	1.23(0.96–1.56)	0.097	1.14(0.88–1.46)	0.321
Others/Unknown	0.92(0.67–1.25)	0.58	1.04(0.76–1.43)	0.809	0.95(0.64–1.39)	0.779	0.99(0.67–1.46)	0.967
Age(years)								
18-49	Reference	–	Reference	–	Reference		Reference	–
≥50	1.63(1.34–1.98)	<0.001	1.49(1.21–1.83)	<0.001	1.05(0.85–1.30)	0.657	1.19(0.95–1.49)	0.129
Marital Status								
Married	Reference	–	Reference	–	Reference	–	Reference	–
Unmarried	1.61(1.39–1.87)	0.001	1.32(1.13–1.54)	<0.001	1.37(1.14–1.65)	0.001	1.18(0.98–1.43)	0.090
Unknown	1.05(0.68–1.61)	0.832	0.96(0.62–1.48)	0.853	0.84(0.48–1.47)	0.549	0.86(0.49–1.51)	0.597
T Stage								
T1	Reference	–	Reference	–	Reference	–	Reference	–
T2	1.62(1.31–2.01)	<0.001	1.54(1.23–1.92)	<0.001	2.27(1.67–3.07)	<0.001	1.95(1.42–2.67)	<0.001
T3	4.38(3.50–5.47)	<0.001	3.63(2.84–4.64)	<0.001	7.03(5.16–9.57)	<0.001	4.96(3.55–6.93)	<0.001
N Stage								
N0	Reference	–	Reference	–	Reference	–	Reference	–
N1	1.44(1.19–1.75)	<0.001	1.48(1.21–1.81)	<0.001	1.93(1.54–2.42)	<0.001	1.73(1.37–2.19)	<0.001
N2-3	3.28(2.61–4.13)	<0.001	2.93(2.30–3.74)	<0.001	4.14(3.19–5.39)	<0.001	3.01(2.28–3.98)	<0.001
Grade								
Well differentiated	Reference	–	Reference	–	Reference	–	Reference	–
Moderately differentiated	1.48(0.93–2.36)	0.099	1.18(0.74–1.89)	0.486	1.23(0.65–2.35)	0.523	0.90(0.47–1.72)	0.740
Poorly differentiated	1.60(1.04–2.46)	0.031	1.37(0.88–2.12)	0.161	2.12(1.19–3.77)	0.011	1.40(0.78–2.53)	0.258
Undifferentiated/Anaplastic	2.09(1.25–3.50)	0.005	1.54(0.91–2.60)	0.108	3.26(1.69–6.29)	<0.001	1.80(0.92–3.51)	0.086
Unknown	2.18(1.38–3.44)	0.001	1.71(1.08–2.71)	0.023	2.45(1.32–4.52)	0.004	1.62(0.87–3.00)	0.130
HR[b] status								
Negative	Reference	–	Reference	–	Reference	–	Reference	–
Positive	0.83(0.69–1.01)	0.066	0.80(0.66–0.98)	0.028	0.87(0.68–1.09)	0.226	0.87(0.68–1.10)	0.238
Borderline/Unknown	1.27(0.98–1.65)	0.068	1.02(0.78–1.33)	0.875	1.42(1.04–1.95)	0.028	1.32(0.95–1.82)	0.096
Surgery								
Mastectomy	Reference	–	Reference	–	Reference	–	Reference	–
BCT	0.43(0.36–0.51)	<0.001	0.76(0.59–0.97)	0.028	0.38(0.31–0.48)	<0.001	0.72(0.53–0.96)	0.026
Radiation								
No	Reference	–	Reference	–	Reference	–	Reference	–
Yes	0.60(0.52–0.70)	<0.001	0.89(0.73–1.10)	0.282	0.68(0.57–0.82)	<0.001	0.92(0.72–1.17)	0.491
Chemotherapy								
No	Reference	–	Reference	–	Reference	–	Reference	–
Yes	0.49(0.42–0.57)	<0.001	0.48(0.40–0.57)	<0.001	0.78(0.65–0.94)	0.010	0.69(0.56–0.85)	0.001

Abbreviations: OS, overall survival; BCSS, breast cancer-specific survival; HR[a], hazard ratios; CI, confidential interval; BCT, breast-conserving therapy; HR[b], hormone receptor.
*With adjustment for race, age, marital status, T stage, N stage, histological grade, hormone receptor status, surgery, radiation and chemotherapy.

approaches for MBC patients in clinical practice. Although a prospective trial would be ideal, it is almost impossible for another such trial to be conducted due to the resource limitations. Besides, we were able to adjust for various confounding factors, including demographics, tumor-related factors and important treatments received. However, there are several limitations in our study. Firstly, as the SEER database is a large database that included 18 tumor registries across the United States, there might existed data-entry errors in our study. Secondly, some patient-related data including geographic location, tumor-related information such as multifocality or multicentricity, molecular genetic features, and surgery of regional lymph nodes could not be accessible, which was another weakness of our study. Thirdly, information concerning local recurrence, distant metastasis and disease-free survival were not routinely reported in the SEER database, thus we could not recognize the patients with breast cancer recurrence who needed more advanced treatments. Forthly, the HER2 status was not mentioned in this study because it was not registered until 2010 [18]. Because most of MBC are HER2-negative, targeted therapy is thought be less likely to influence the survival.

In conclusion, by using the SEER database which contained information from a widespread population throughout the United States, we investigated the relationship between survival outcomes and surgical approaches for patients with early-stage MBC. Our study demonstrated that BCT conferred superior OS and BCSS compared with mastectomy for patients with early-stage MBC, and the improvement persisted in almost all of the subgroups of AJCC T and N stages, providing the knowledge in decision-making of surgical options for patients with early-stage MBC.

Statement of ethics

This study was exempt from the approval of the Institutional Review Boards because patient information of the SEER database is de-identified. The SEER program approved the use of these data without the need for individual subject consent.

Funding sources

This study is supported by grants from National Natural Science Foundation of China (Grant No. 81871513), Science and Technology Planning Project of Guangzhou City (202002030236), Science and Technology Special Fund of Guangdong Provincial People's Hospital (No.Y012018218), CSCO-Hengrui Cancer Research Fund (Y-HR2016-067) and Guangdong Provincial Department of Education Characteristic Innovation Project (2015KTSCX080).

Author contributions

J-SZ, C-QY and C-QL were involved in the design and coordination of the study as well as in data analysis, interpretation of results, and drafting the manuscript. KW was in charge of all study procedures. The others participated in the study procedures and critically revised the content of the manuscript. All authors contributed to the data analysis, gave final approval of the manuscript to be submitted, and agreed to be accountable for all aspects of the work.

Declaration of competing interest

None.

Acknowledgements

The authors acknowledge the efforts of the Surveillance, Epidemiology, and End Results (SEER) program registries in the creation of the SEER database.

References

[1] Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233–41.
[2] Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227–32.
[3] Arriagada R, Lê MG, Rochard F, Contesso G. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. J Clin Oncol : Off J Am Soc Clin Oncol 1996;14:1558–64.
[4] Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet (London, England) 2005;366:2087–106.
[5] Litière S, Werutsky G, Fentiman IS, Rutgers E, Christiaens M-R, Van Limbergen E, et al. Breast conserving therapy versus mastectomy for stage I–II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. Lancet Oncol 2012;13:412–9.
[6] Hwang ES, Lichtensztajn DY, Gomez SL, Fowble B, Clarke CA. Survival after lumpectomy and mastectomy for early stage invasive breast cancer: the effect of age and hormone receptor status. Cancer 2013;119:1402–11.
[7] Agarwal S, Pappas L, Neumayer L, Kokeny K, Agarwal J. Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer. JAMA Surg 2014;149:267–74.
[8] Hartmann-Johnsen OJ, Kåresen R, Schlichting E, Nygård JF. Survival is better after breast conserving therapy than mastectomy for early stage breast cancer: a registry-based follow-up study of Norwegian women primary operated between 1998 and 2008. Ann Surg Oncol 2015;22:3836–45.
[9] Lagendijk M, van Maaren MC, Saadatmand S, Strobbe LJA, Poortmans PMP, Koppert LB, et al. Breast conserving therapy and mastectomy revisited: breast cancer-specific survival and the influence of prognostic factors in 129,692 patients. Int J Canc 2018;142:165–75.
[10] Fisher S, Gao H, Yasui Y, Dabbs K, Winget M. Survival in stage I-III breast cancer patients by surgical treatment in a publicly funded health care system. Ann Oncol 2015;26:1161–9.
[11] van Maaren MC, de Munck L, Jobsen JJ, Poortmans P, de Bock GH, Siesling S, et al. Breast-conserving therapy versus mastectomy in T1-2N2 stage breast cancer: a population-based study on 10-year overall, relative, and distant metastasis-free survival in 3071 patients. Breast Canc Res Treat 2016;160:511–21.
[12] van Maaren MC, de Munck L, de Bock GH, Jobsen JJ, van Dalen T, Linn SC, et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in The Netherlands: a population-based study. Lancet Oncol 2016;17:1158–70.
[13] Beatty JD, Atwood M, Tickman R, Reiner M. Metaplastic breast cancer: clinical significance. Am J Surg 2006;191:657–64.
[14] Gibson GR, Qian D, Ku JK, Lai LL. Metaplastic breast cancer: clinical features and outcomes. Am Surg 2005;71:725–30.
[15] Toumi Z, Bullen C, Tang AC, Dalal N, Ellenbogen S. Metaplastic breast carcinoma: a case report and systematic review of the literature. Pathol Int 2011;61:582–8.
[16] Pezzi CM, Patel-Parekh L, Cole K, Franko J, Klimberg VS, Bland K. Characteristics and treatment of metaplastic breast cancer: analysis of 892 cases from the National Cancer Data Base. Ann Surg Oncol 2007;14:166–73.
[17] Tray N, Taff J, Adams S. Therapeutic landscape of metaplastic breast cancer. Canc Treat Rev 2019;79:101888.
[18] Schroeder MC, Rastogi P, Geyer Jr CE, Miller LD, Thomas A. Early and locally advanced metaplastic breast cancer: presentation and survival by receptor status in surveillance, Epidemiology, and End results (SEER) 2010-2014. Oncol 2018;23:481–8.
[19] Nelson RA, Guye ML, Luu T, Lai LL. Survival outcomes of metaplastic breast cancer patients: results from a US population-based analysis. Ann Surg Oncol 2015;22:24–31.
[20] Leyrer CM, Berriochoa CA, Agrawal S, Donaldson A, Calhoun BC, Shah C, et al. Predictive factors on outcomes in metaplastic breast cancer. Breast Canc Res Treat 2017;165:499–504.
[21] Bian T, Lin Q, Wu Z, Cui C, Qi C, Li L, et al. Metaplastic carcinoma of the breast: imaging and pathological features. Oncol Lett 2016;12:3975–80.
[22] Edenfield J, Schammel C, Collins J, Schammel D, Edenfield WJ. Metaplastic breast cancer: molecular typing and identification of potential targeted therapies at a single institution. Clin Breast Canc 2017;17:e1–10.
[23] Jung SY, Kim HY, Nam BH, Min SY, Lee SJ, Park C, et al. Worse prognosis of metaplastic breast cancer patients than other patients with triple-negative breast cancer. Breast Canc Res Treat 2010;120:627–37.
[24] Bae SY, Lee SK, Koo MY, Hur SM, Choi MY, Cho DH, et al. The prognoses of metaplastic breast cancer patients compared to those of triple-negative breast cancer patients. Breast Canc Res Treat 2011;126:471–8.
[25] He X, Ji J, Dong R, Liu H, Dai X, Wang C, et al. Prognosis in different subtypes of metaplastic breast cancer: a population-based analysis. Breast Canc Res Treat 2019;173:329–41.
[26] Tseng WH, Martinez SR. Metaplastic breast cancer: to radiate or not to radiate? Ann Surg Oncol 2011;18:94–103.
[27] https://www.census.gov/quickfacts/fact/note/US/RHI425219.
[28] Abouharb S, Moulder S. Metaplastic breast cancer: clinical overview and molecular aberrations for potential targeted therapy. Curr Oncol Rep 2015;17:431.
[29] Cimino-Mathews A, Verma S, Figueroa-Magalhaes MC, Jeter SC, Zhang Z, Argani P, et al. A clinicopathologic analysis of 45 patients with metaplastic breast carcinoma. Am J Clin Pathol 2016;145:365–72.
[30] Rayson D, Adjei AA, Suman VJ, Wold LE, Ingle JN. Metaplastic breast cancer: prognosis and response to systemic therapy. Ann Oncol 1999;10:413–9.
[31] Taube JH, Herschkowitz JI, Komurov K, Zhou AY, Gupta S, Yang J, et al. Core epithelial-to-mesenchymal transition interactome gene-expression signature is associated with claudin-low and metaplastic breast cancer subtypes. Proc Natl Acad Sci U S A 2010;107:15449–54.
[32] Hennessy BT, Gonzalez-Angulo AM, Stemke-Hale K, Gilcrease MZ, Krishnamurthy S, Lee JS, et al. Characterization of a naturally occurring breast cancer subset enriched in epithelial-to-mesenchymal transition and stem cell characteristics. Canc Res 2009;69:4116–24.
[33] Eskander MF, Schapira EF, Bliss LA, Burish NM, Tadikonda A, Ng SC, et al. Keeping it in the family: the impact of marital status and next of kin on cancer treatment and survival. Am J Surg 2016;212:691–9.
[34] Haque W, Verma V, Naik N, Butler EB, Teh BS. Metaplastic breast cancer: practice patterns, outcomes, and the role of radiotherapy. Ann Surg Oncol 2018;25:928–36.