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Original Article

Triple-negative metaplastic breast cancer: treatment and prognosis by type of surgery

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Abstract: Background: The role of surgery type in the prognosis of triple-negative metaplastic breast cancer (TN-MBC) patients remains controversial. Our study was designed to assess the role of surgery type in patient outcomes. Materials and methods: Data from the Surveillance, Epidemiology, and End Results database were extracted to analyze patients with TN-MBC between 2010 and 2016. Kaplan-Meier analyses and multivariate Cox proportional models were used to estimate the prognoses. Results: We included 1,146 patients with a median follow-up time of 26 months (range 1-83 months). 470 (41.0%), 369 (32.2%), 244 (21.3%), and 63 (5.5%) patients underwent breast-conserving surgery (BCS), total mastectomy (TM), radical mastectomy, or no surgery. With the multivariate Cox analysis, the prognosis was related to age, TNM stage, and surgery type. With the Kaplan-Meier analysis, the more radical the operation, the worse the prognosis for the patients in the entire cohort. Within stage I-III disease, the best prognoses were observed in the patients undergoing BCS, followed by TM and radical mastectomy. The adjusted survival analysis showed that the prognoses of the patients undergoing BCS were better than the prognoses of the patients undergoing TM. Within stage IV disease, the patients who underwent an operation had a better prognosis regardless of the mode. Conclusion: Patients undergoing BCS had the best prognoses among the patients with early and locally advanced TN-MBC. This improves our understanding of the clinicopathological and prognostic features of this rare entity but also provides more convincing therapeutic guidelines for TN-MBC.

Keywords: Metaplastic, breast cancer, surgery, prognosis, inverse probability weights

Introduction

The World Health Organization recognized metaplastic breast cancer (MBC) as a unique histologic subtype in 2000 [1]. MBC is a rare histologic subtype and represents approximately 2-5% of breast cancers diagnosed annually [2]. Previous studies classified MBC into five subtypes: squamous cell carcinoma, spindle cell carcinoma, carcinosarcoma, matrix-producing carcinoma, and metaplastic carcinoma with osteoclastic giant cells [3-7]. MBC tends to present with unique characteristics: a greater frequency of T3 or T4 disease, less involvement of the regional lymph nodes, and a greater frequency of the triple-negative type [8-10].

Of note, the treatment for MBC is largely similar to the treatment for infiltrating ductal carcinoma (IDC) [11]. However, MBC patients have worse outcomes than IDC even after undergoing comprehensive treatment [12, 13]. Recently, researchers found that patients with MBC have a worse prognosis, with their 5-year survival rates ranging from approximately 30 to 70%. Such a low survival rate might be the cause that approximately 65-80 percentage of MBC patients have the triple-negative phenotype [14, 15]. Furthermore, Yaming Li [16] reported that the overall survival and disease-free survival of the triple-negative MBC (TN-MBC) were worse than the triple-negative IDC (TN-IDC). Xuexin He found that the prognosis of TN-MBC is worse than the prognoses of MBC and non-triple negative MBC (non-TN MBC) [9].

Despite this worse survival and the challenges of the treatment, there are no current, specifical therapeutic guidelines for MBC patients.

Table 1. Stepwise inclusion and exclusion counts

2010-2016 MBC patients	0	2240
Exclude men	6	2234
Exclude patients younger than 18 years	2	2232
Exclude patients with non-TN MBC	829	1403
Exclude patients without histology or cytology confirmation	2	1401
Exclude patients whose tumor was not the first tumor	172	1229
Exclude patients with bilateral involvement	2	1227
Exclude patients without survival information/diagnosed by autopsy/death record only	81	1146
Final data set	0	1146

Surgery is the appropriate first step in the treatment of malignant tumors. Breast-conserving surgery (BCS) is performed. But many patients have received some type of mastectomy according to the surgical and pathologic literature. There is no consensus in the previous studies regarding the effect of the breast surgery type on the prognosis [17, 18]. Our study aimed to explore the best surgery type for TN-MBC.

Materials and methods

Database and population

Data from 2010 to 2016 were obtained from Surveillance, Epidemiology, and End Results (SEER) database. We extracted the demographic, clinical and pathological information from the database. The metaplastic histology was identified with the international classification of diseases for oncology Version 3 (ICD-O-3) codes: 8560, 8562, 8570-8572, 8575, and 8980-8982. Altogether, 1,146 patients were enrolled. The inclusion criteria are shown in **Table 1**.

Demographic and clinicopathologic variables

The demographic and clinicopathologic parameters included age, race/ethnicity, insurance, marital state, grade, tumor size, regional lymph node status, chemotherapy, radiotherapy, and surgery type (BCS, total mastectomy [TM], radical mastectomy, and non-surgery). The TNM stage was determined according to the sixth/seventh editions of the American Joint Committee on Cancer pathologic staging system. The breast cancer-specific survival (BCSS) from the date of diagnosis to the date of death caused by MBC was the clinical outcome.

Statistical analysis

Data were expressed as the mean ± standard deviation and as the number of subjects and percentages. The risk factors for survival were identified using the Cox proportional hazards model. The hazard ratio (HR) and 95% confidence index (95% CI) were calculated. Significance was set at a 2-tailed *P*-value <0.05. The Kaplan-Meier analysis and log-rank testing were used for the BCSS curves. Four curves applied pairwise comparisons with Bonferroni corrections [19]. Statistical significance was defined as a 2-tailed *P*-value <0.0083 (0.05/6). The statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) and the 'IPW survival' and 'rms' packages in R version 3.6.1 (http://www.r-project.org/).

Since the patient information in the SEER database was not identified, this study was not subject to the approval procedure of the Institutional Review Boards. In addition, a patient consent form was not applicable.

Result

Patient characteristics

The SEER registry recorded 2,240 MBC patients between 2010 and 2016. Our final sample comprised 1,146 patients. **Table 2** shows the characteristics of the study population. The majority of the patients were white (76.5%) women. TN-MBC were most common poorly differentiated (69.4%), although 11.7% had an unknown tumor grade. Many patients had stage II (58.7%), followed by stage I (22.8%) and stage III (13.6%). Some patients underwent chemotherapy (67.0%) and radiotherapy (44.3%). 470 (41.0%), 369 (32.2%), 244 (21.3%), and 63 (5.5%) of the patients under-

Table 2. The clinical and pathologic characteristics of TN-MBC

Variables	N	%
Age (median, range)	62 (22-89)	-
Race/ethnicity (n, %)		
White	877	76.5
Black	190	16.6
Other	79	6.9
Insurance (n, %)		
No	189	16.5
Yes	957	83.5
Marital state (n, %)		
Unmarried	268	23.4
Married	878	76.6
Grade (n, %)		
Undifferentiated	34	3.0
Poorly differentiated	795	69.4
Moderately differentiated	132	11.5
Well differentiated	51	4.5
Unknown	134	11.7
Tumor size (n, %)		
T1	289	25.2
T2	550	48.0
T3	202	17.6
T4	56	4.9
Regional node status (n, %)		
N0	918	80.1
N1	170	14.8
N2	33	2.9
N3	25	2.2
TNM stage (n, %)		
I	261	22.8
II	673	58.7
III	156	13.6
IV	56	4.9
Chemotherapy (n, %)		
No	378	33.0
Yes	768	67.0
Radiotherapy (n, %)		
No	638	55.7
Yes	508	44.3
Surgery mode (n, %)		
No surgery	63	5.5
BCS	470	41.0
TM	369	32.2
Radical mastectomy	244	21.3

Abbreviations: MBC = metaplastic breast cancer; BCS = breast conserving surgery; TM = Total mastectomy.

went BCS, TM, radical mastectomy, or no surgery, respectively.

Prognostic factors for breast cancer-specific survival

The univariate factors associated with BCSS included age (P=0.012), race/ethnicity (P=0.048), marital status (P=0.020), TNM stage (P<0.01), radiotherapy (P=0.005), and surgery type (P<0.01). In order to eliminate the confounding factors, the variables with a P value less than 0.1 and with a clinical value were included in the multivariate analysis model. Age (HR 1.022, 95% CI 1.010-1.034, P<0.001), TNM stage (stage I as the reference; stage II, HR 1.704, 95% CI, 1.003-2.894; P=0.049; stage III, HR 4.636, 95% CI 2.570-8.363, P<0.001; stage III, HR 20.267, 95% CI 11.096-37.016, P<0.001), and surgery type (BCS as the reference; TM, HR 1.747, 95% CI 1.138-2.683, P=0.011; radical mastectomy, HR 2.803, 95% CI 1.837-4.277, P<0.001; no surgery, HR 5.991, 95% CI 3.384-10.606, P<0.001) were independent prognostic factors (**Table 3**).

Survival analysis

As shown on the Kaplan-Meier survival curves, the more radical the operation, the worse the prognosis for the patients in the entire cohort (all P<0.001). Within stage I-III disease, the best prognosis was seen in the patients undergoing BCS, followed by TM and radical mastectomy, but there was no difference in the outcomes among the patients undergoing radical mastectomy and the patients not undergoing surgery (BCS vs. TM, P=0.0011; TM vs. radical mastectomy, P<0.001; radical mastectomy vs. non-surgery, P=0.424). Within stage IV disease, the patients who underwent BCS or TM had better prognoses, compared with the non-surgery group. However, there was no difference in the prognoses between the radical mastectomy group and the non-surgery group (BCS vs. TM, P=0.496; BCS vs. radical mastectomy, P=0.168; BCS vs. non-surgery, P<0.001; TM vs. radical mastectomy, P=0.380; TM vs. non-surgery, P=0.0021; radical mastectomy vs. non-surgery, P=0.0141) (**Figure 1**).

Adjusted Kaplan-Meier survival analysis

Adjuvant radiotherapy is an essential part of the treatment after BCS for breast cancer patients. To eliminate the influence of the confounding factors, including age and race/ethnicity, and especially radiotherapy, we performed an adjusted Kaplan-Meier survival analy-

Table 3. The prognostic factors for BCSS in our TN-MBC

Variables	Univariate analysis		*P*	Multivariate analysis		*P*
	HR	95% CI		HR	95% CI	
Age (median, range)	1.013	1.003-1.023	0.012	1.022	1.010-1.034	<0.001
Race/ethnicity (n, %)						
Black	1	[reference]		1	[reference]	
White	0.712	0.508-0.997	0.048	0.721	0.506-1.028	0.070
Other	0.784	0.436-1.412	0.418	0.742	0.407-1.353	0.330
Insurance (n, %)						
No	1	[reference]		1	[reference]	
Yes	0.728	0.523-1.014	0.061	0.776	0.550-1.096	0.150
Marital state (n, %)						
Unmarried	1	[reference]		1	[reference]	
Married	0.701	0.521-0.945	0.020	0.843	0.617-1.153	0.286
Grade (n, %)						
Undifferentiated	1	[reference]		1	[reference]	
Poorly differentiated	0.616	0.325-1.169	0.139	0.623	0.324-1.198	0.156
Moderately differentiated	0.345	0.153-0.777	0.010	0.406	0.178-0.922	0.031
Well differentiated	0.453	0.179-1.149	0.096	0.991	0.378-2.599	0.985
Unknown	0.862	0.427-1.741	0.687	0.690	0.336-1.420	0.314
TNM stage (n, %)						
I	1	[reference]		1	[reference]	
II	2.186	1.320-3.619	0.002	1.704	1.003-2.894	0.049
III	7.621	4.495-12.920	<0.001	4.636	2.570-8.363	<0.001
IV	29.625	16.987-51.668	<0.001	20.267	11.096-37.016	<0.001
Chemotherapy (n, %)						
No	1	[reference]		1	[reference]	
Yes	0.996	0.728-1.282	0.812	0.984	0.710-1.365	0.924
Radiotherapy (n, %)						
No	1	[reference]		1	[reference]	
Yes	0.675	0.513-0.887	0.005	1.003	0.734-1.372	0.983
Surgery mode (n, %)						
BCS	1	[reference]		1	[reference]	
TM	2.125	1.422-3.175	<0.001	1.747	1.138-2.683	0.011
Radical mastectomy	4.753	3.274-6.898	<0.001	2.803	1.837-4.277	<0.001
No surgery	9.979	6.100-16.326	<0.001	5.991	3.384-10.606	<0.001

Abbreviations: MBC = metaplastic breast cancer; BCS = breast conserving surgery; TM = total mastectomy.

sis with inverse probability weights (IPW). After adjusting the confounding factors, including age, race/ethnicity, marital status, and radiotherapy, the difference was still present between BCS and TM for the patients with stages I-III disease (**Figure 2**).

Discussion

In the present study, we assessed the prognostic factors, and our results found that patients undergoing BCS have superior prognoses in early and locally advanced TN-MBC. This difference remained significant in the adjusted survival curves. Within stage IV disease, patients can benefit from BCS or TM, regardless of the mode.

Specifically, compared with the IDC patients with negative receptors, the MBC patients with negative receptors have a larger proportion of undifferentiated and poorly differentiated tumors, higher T-classifications, and more advanced disease, and they underwent chemo-

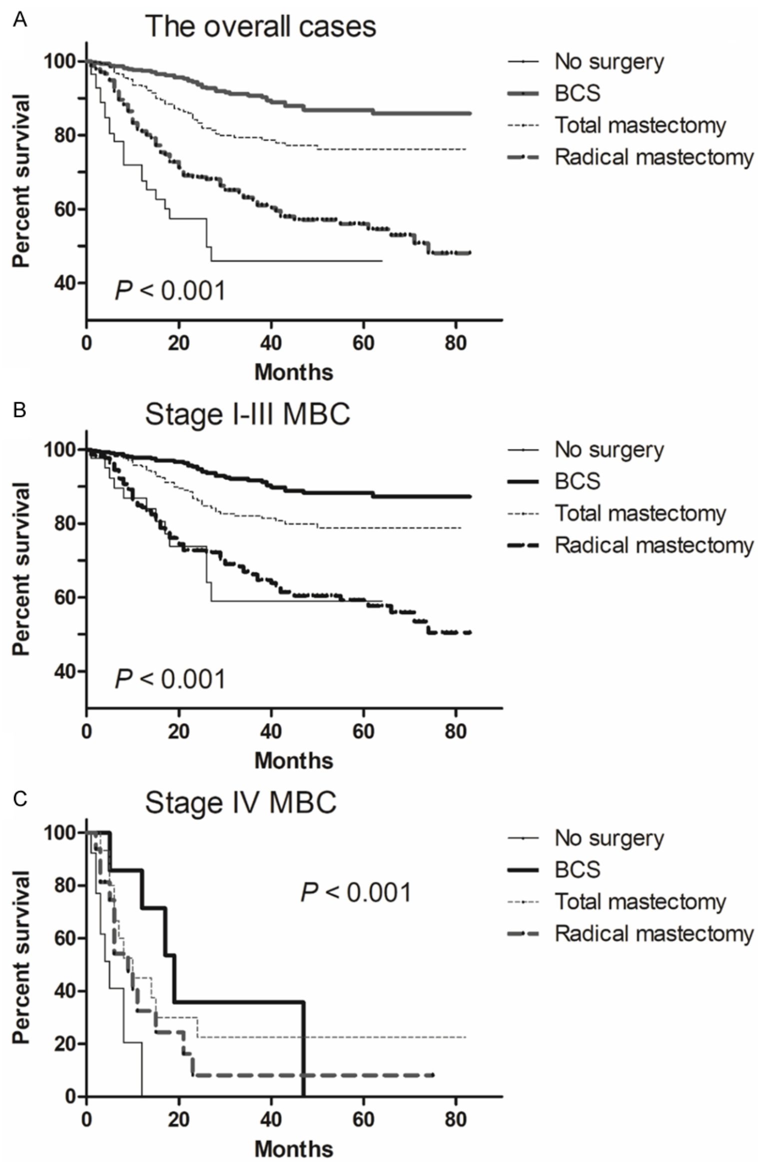

Figure 1. The breast cancer-specific survival for MBC with the different surgery types. Abbreviations: MBC = metaplastic breast cancer; BCS = breast-conserving surgery.

therapy more frequently [20]. In addition, due to their higher number of subtypes of triple-negative tumors and their larger tumor sizes, those patients may undergo total mastectomies or radical mastectomies more often.

It is difficult to perform case-control studies because of the low incidence of this rare disease. Our study aimed to explore the best surgery type for TN-MBC. The involvement of surgery in MBC patient prognosis has been described. On the one hand, a previously published study suggested that surgery can improve the prognosis, but the mode of surgery was not mentioned [9]. On the other hand, some researchers only paid attention to the lumpectomy and mastectomy surgery types. Some of them showed that the type of surgery was not a prognostic factor for disease-specific survival or overall survival [11, 15, 21, 22]. Others found that patients who underwent mastectomies had a worse outcome than the patients who underwent lumpectomies [23, 24]. BCS plus postoperative radiotherapy is regarded as the standard treatment for early-stage breast cancer. Some authors suggested that the MBC patients who underwent a mastectomy or a lumpectomy had a worse overall survival than the patients who underwent a lumpectomy with radiotherapy [20, 24, 25].

However, to our knowledge, we are the first to investigate the association between surgery type and prognosis. The patients are grouped according to their surgery type classification, including the BCS group, the TM group, the radical mastectomy group, and the no surgery group. Our results showed that the patients who underwent BCS had the best prognosis in early and locally advanced TN-MBC. Even though adjusted survival analyses were performed with IPW, the difference between BCS and TM remained significant for the early and locally advanced TN-MBC patients.

Kaplan-Meier survival curves and the related log-rank tests are part of the unadjusted survival analysis, but semiparametric Cox proportional hazards regression models as covariate adjustment methods are widely used. Cole [26] described a method for establishing an adjusted survival curve using IPW. Since age

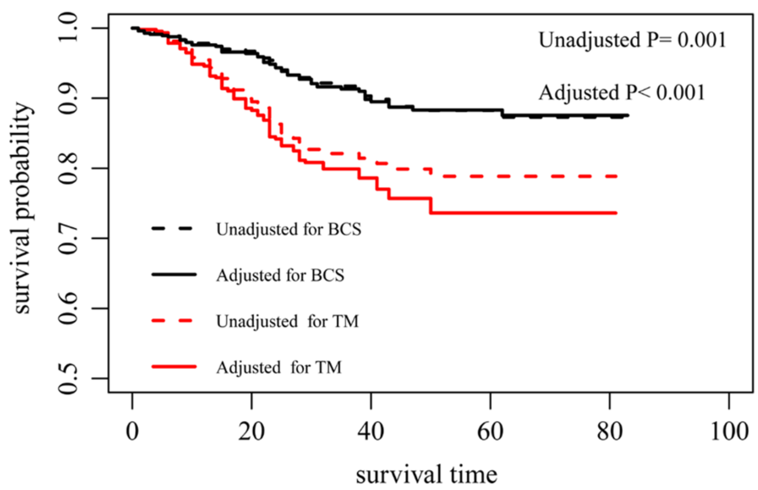

Figure 2. Unadjusted and Adjusted Kaplan-Meier survival estimates for BCSS in TN-MBC with stages I-III. Adjusting for the confounding factors includes the following variables: age, race/ethnicity, marital status, radiotherapy. Abbreviation: MBC = metaplastic breast cancer.

and race/ethnicity are associated with prognosis, especially radiotherapy, which was not only related to BCSS but are also relevant to surgery type, we performed an adjusted Kaplan-Meier survival analysis with IPW to eliminate the influence of the confounding factors. The adjusted survival curve showed the prognosis of the BCS group remains better than the prognosis of the TM group.

Xuexin He [9] reported that TN-MBC had the worst of the worst prognosis after comparing it with the outcomes of IDC, MBC, TN-MBC, non-TN MBC, and non-MBC triple-negative breast cancer (non-MBC TNBC). The tumors are enriched in stem-like features and the epithelial-to-mesenchymal transition, which might provide an explanation for the poorer prognosis of TN-MBC [27, 28]. According to the National Comprehensive Cancer Network (NCCN) guidelines [29], treatment for TN-MBC is parallel to traditional triple-negative breast carcinoma, which might also be closely correlated to a poorer prognosis. Yaming Li [16] reported that compared with the patients with traditional TNBC, the prognosis of patients with TN-MBC had a poorer overall survival and a poorer disease-free survival. They speculated that the poorer prognosis was associated with increasing age, larger tumor size, and less chemotherapy management.

There are several limitations to our study. First, the database we used lacked baseline characteristics, including performance status, comorbidity, and socio-economic environment. Second, the SEER database lacked information on the specific rugs treatment, the chemotherapy regimen, and the radiotherapy dose and target volume. Third, there was the possibility of selection bias for a retrospective study.

Our study also has several strengths. First, this is the first detailed study on the impact of surgery type on prognosis in TN-MBC patients. Second, to eliminate the influence of the confounding factors between BCS and TM, including age and race/ethnicity and especially radiotherapy, we performed an adjusted Kaplan-Meier survival analysis with IPW. The results might contribute to the current knowledge on the MBC management strategy.

Despite those limitations, our study is a step forward in defining the prognosis of MBC with different surgery types. Based on our study, clinicians can better choose an effective surgery type. Our results show that the prognoses of patients undergoing breast-conserving surgery is better than the prognoses of total mastectomy and radical mastectomy patients for early and locally advanced TN-MBC.

Conclusion

With the development of medical technology, breast cancer surgery has become less radical, starting with radical mastectomy through modified radical mastectomy to BCS. However, the role of surgery type in the outcomes of patients with TN-MBC remains controversial. Our results not only improve our understanding of the clinicopathological and prognostic features of this rare entity but also provide more convincing treatment options for TN-MBC.

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Disclosure of conflict of interest

None.

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