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Research article

Breast conserving surgery (BCS) with adjuvant radiation therapy showed improved prognosis compared with mastectomy for early staged triple negative breast cancer patients

Running title: BCS had better prognosis than mastectomy for early TNBC patients

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Abstract: *Background*: Triple-negative breast cancer (TNBC) is a subtype of breast cancer with stronger invasive capacity. For the operation strategies of early staged (stage I and stage II) TNBC patients, BCS plus radiotherapy (BCS+RT), mastectomy only (MRM only) or MRM plus radiotherapy (MRM+RT) is feasible, but no clear conclusion has been made on the choice of these treatments.
Methods: The early staged TNBC patients (stage I and stage II) from the Surveillance, Epidemiology and End Results (SEER) program database between 1973 and 2014 were included in the study.

Survival curves, univariate and multivariate cox proportional hazards models and propensity score weighting were applied to evaluate the prognostic impact among BCS+RT, MRM only and MRM+RT for patients.

Results: Both overall and cancer-specific survival analysis showed that BCS+RT had better prognostic effect than MRM and MRM+RT in the cohort of early-staged triple-negative breast cancer patients (overall survival, $P < 0.001$; cancer-specific survival, $P < 0.001$). By taking all the risk factors into a multivariate cox proportional model, MRM and MRM+RT remained to have detrimental effect on the prognosis compared with BCS+RT as shown by either overall (HR = 1.742, CI = 1.387–2.188, $P < 0.001$; HR = 1.449, CI = 1.038–2.204, $P = 0.029$) or cancer-specific survival (HR = 1.876, CI = 1.415–2.489, $P < 0.001$; HR = 1.701, CI = 1.168–2.478, $P = 0.006$). After we performed propensity score weighting and integrated the weights for each covariate in the multivariate cox proportional model. BCS+RT remained to be prognostic beneficial compared to the other treatment options ($P < 0.001$).

Conclusion: BCS+RT demonstrated better prognosis than MRM only and MRM+RT treatments for early-staged TNBC patients.

Keywords: triple-negative breast cancer (TNBC); radiotherapy; breast conserving surgery (BCS); mastectomy; propensity score matching (PSM)

1. Introduction

Breast cancer is the most frequent female cancer and the second common cause of female cancer death in the world [1]. Triple-negative breast cancer (TNBC), defined by the lack of protein expression of estrogen receptor (ER), progesterone receptor (PR) and HER2, is a subtype of breast cancer with stronger invasive capacity compared with the other subtypes and comprises 15–20% of all breast cancers [2,3]. A study with 15,204 women from National Comprehensive Cancer Network (NCCN) centers showed that TNBC was associated with a greater risk of brain or lung metastases and had worse cancer-specific and overall survival [4]. The major treatment of TNBC is chemotherapy according to the NCCN guide, but the adjuvant radiotherapy can also improve the prognosis of patients with triple-negative breast cancer [5]. For the operation strategies of early staged (stage I and stage II) TNBC patients, breast conserving surgery (BCS) and mastectomy are both feasible [6,7]. A randomized controlled trail (RCT) recently indicated that long-term survival rate among women who underwent breast-conserving surgery is similar to those received radical mastectomy [8]. Previous studies have been conducted to explore the causal relationship between different treatments and survival of TNBC patients [9–14]. However, no clear conclusion has been made on the choice of BCS or mastectomy due to the limited study population or different geographic locations. BCS is more acceptable to patients with TNBC considering the postoperative influence on life quality and constant advancement of medical techniques. Given that radiotherapy was usually conducted together with BCS, we conducted the present study on early staged TNBC patients to compare the prognosis among BCS plus radiotherapy (BCS+RT), mastectomy only

(MRM only) and MRM plus radiotherapy (MRM+RT) in order to explore whether it is possible to reduce the scope of surgery in early staged TNBC patients.

2. Materials and methods

2.1. Ethics statement

A Data-Use Agreement for the Surveillance, Epidemiology and End Results (SEER) 1973–2014 Research Data File was completed for the access of the 18 population-based registries of breast cancer patients included in our study.

The SEER database was downloaded from the official website (http://seer.cancer.gov/about/overview.html). Primary breast cancer with histology of "triple negative" were considered in the study. Radiation and chemotherapy information were retrieved individually after getting approval from the SEER official. Surgery methods were classified based on the SEER site-specific surgery codes with 20–24 as receiving breast-conserving surgery (BCS), and 30–80 were categorized as receiving mastectomy. We only considered patients with stage I or II triple-negative breast cancer in the study. Besides, we also considered age at diagnosis, race, registry, tumor grade, tumor size, lateral of original tumor, number of lymph nodes examined, nodal status, chemotherapy and radiation for each patient. Patients were grouped into three age groups as less than 45 years old, 45 to 65 years and more than 65 years old. Race-based classification included American Indian/Alaska Native (AI/AN), Asian, Black and White. The 18 registries were grouped into three classes, central (Metropolitan Detroit, Iowa, Kentucky, Utah and Louisiana), east (New Jersey, Metropolitan Atlanta, Rural Georgia and Greater Georgia) and west (Alaska, Greater California, Hawaii, Los Angeles, New Mexico, San Francisco-Oakland SMSA, San Jose-Monterey and Seattle), according to the geographical location. All tumor grades were considered as well differentiated (G1), moderately differentiated (G2), poorly differentiated (G3) or undifferentiated (G4). Three categories of tumor size were grouped by cutoffs of 2 and 10 cm. The number of lymph nodes examined were split by 12, a commonly used standard in practice. Patients with no available information of the considered clinical characteristics or survival information were excluded from the following analysis, which resulted in the final dataset with 6,342 early-staged triple-negative breast cancer patients.

2.2. Propensity score weighting

We applied propensity score weighting to estimate balancing weights for each treatment group in order to eliminate the selection bias of the study population. Balancing weight was calculated by constructing a multivariate logistic model including age at diagnosis, race, registry, tumor grade, tumor size, lateral of original tumor, number of lymph nodes examined, nodal status and chemotherapy. The estimated weights for each treatment was next included in the multivariate cox proportional model for prognostic prediction. R package "WeightIt" was used for this analysis, and the covariate balancing propensity score weighting (cbps) algorithm was applied in the model.

2.3. Statistical analysis

The statistical analysis in this work were conducted with R version 3.5.1. Chi-square ($\chi 2$) test were conducted on all the clinicopathological characteristics undergoing BCS or mastectomy before and after the propensity score matching. Survival curves were generated by Kaplan-Meier and log-rank test was applied to calculate difference between the curves. Univariate and multivariate cox proportional hazards models were applied for estimating hazard ratios (HRs) and 95% confidence intervals (CI) for each variate by the R package "survival". All statistical tests were two-sided and significant difference was considered as p-value less than 0.05.

3. Results

3.1. Overview of the study population

Among the 6,269 early-staged triple-negative breast cancer patients included in the study, 59.1% received radiotherapy and 60.5% had BCS, which both showed positive effects on the prognosis (Table S1). The prognostic value of both surgery and radiotherapy remained after excluding the impact of covariates (Table S2). BCS was always accompanied with RT in both our dataset and clinical practice, and post-mastectomy RT is not always indicated for patients undergoing mastectomy, we here evaluated the different prognosis among three treatment groups (BCS+RT, MRM only and MRM+RT). The demographic and clinical prognosticators across the three groups were shown in Table 1. All the characteristics had significant biases between these groups except for lateral location (Table 1).

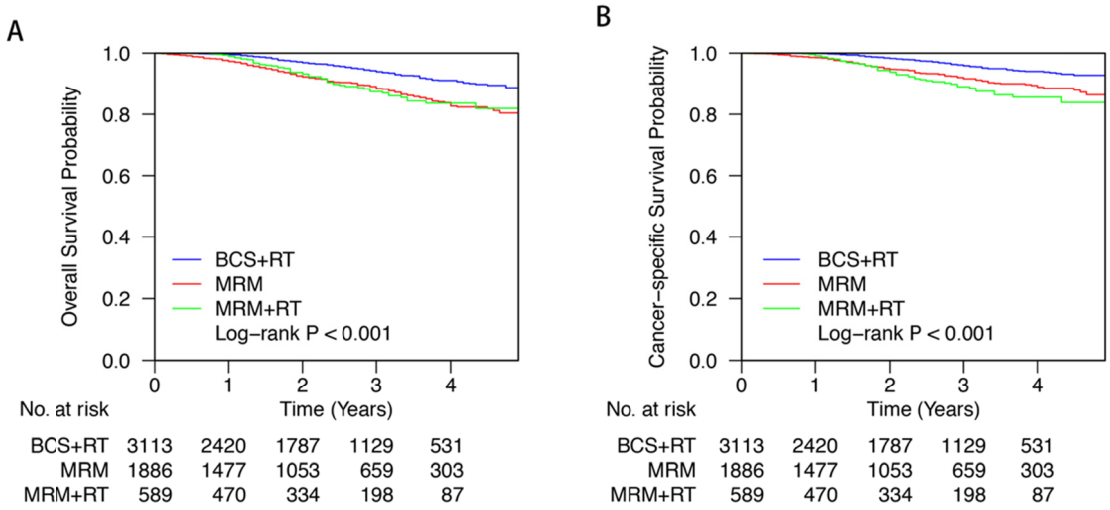

Figure 1. Patients with BCS+RT therapy had significantly better overall and cancer-specific survival probability compared with those who did MRM and MRM+RT (overall survival, $P < 0.001$; cancer-specific survival, $P < 0.001$).

Table 1. Demographic and clinical characteristics of patients with early-staged triple-negative breast cancer among three groups.

Characteristics	BCS+RT	MRM	MRM+RT	P-value
number	3113	1886	589	
Age (%)				<0.001
<45	385 (12.4)	441 (23.4)	180 (30.6)	
>65	936 (30.1)	522 (27.7)	90 (15.3)	
45–65	1792 (57.6)	923 (48.9)	319 (54.2)	
Chemotherapy (%)				<0.001
Chemotherapy+	2440 (78.4)	1322 (70.1)	553 (93.9)	
Chemotherapy–	673(21.6)	564(29.9)	36(6.1)	
Radiation (%)				<0.001
Radiation+	3113 (100.0)	0 (0.0)	589 (100.0)	
Radiation–	0 (0.0)	1886 (100.0)	0(0.0)	
Stage (%)				<0.001
I	1662(53.4)	760(40.3)	44(7.5)	
II	1451 (46.6)	1126 (59.7)	545 (92.5)	
Surgery				<0.001
BCS	3113 (100.0)	0 (0.0)	0(0.0)	
mastectomy	0 (0.0)	1886 (100.0)	589 (100.0)	
Tumor Size (%)				<0.001
<2 cm	1743 (56.0)	819 (43.4)	128 (21.7)	
2–10 cm	1369 (44.0)	1062 (56.3)	457 (77.6)	
>10 cm	1 (0.0)	5 (0.3)	4 (0.7)	
Grade (%)				<0.001
Well differentiated	90 (2.9)	42 (2.2)	8 (1.4)	
Moderately differentiated	558 (17.9)	331 (17.6)	75 (12.7)	
Poorly differentiated	2459 (79.0)	1498 (79.4)	504 (85.6)	
Undifferentiated	6 (0.2)	15 (0.8)	2 (0.3)	
Race (%)				0.001
AI/AN	20 (0.6)	15 (0.8)	5 (0.8)	
Asian	259 (8.3)	196 (10.4)	61 (10.4)	
black	644 (20.7)	302 (16.0)	118 (20.0)	
white	2190 (70.4)	1373 (72.8)	405 (68.8)	
Registry (%)				0.047
central	1212 (38.9)	676 (35.8)	230 (39.0)	
east	680 (21.8)	478 (25.3)	132 (22.4)	
west	1221 (39.2)	732 (38.8)	227 (38.5)	
Lateral (%)				0.195
Left	1478(47.5)	924(49.0)	302(51.3)	
Right	1635 (52.5)	962 (51.0)	287 (48.7)	
Lymph nodes examined (%)				<0.001
<12	2815(90.4)	1618(85.8)	371(63.0)	
>=12	298 (9.6)	268 (14.2)	218 (37.0)	
Lymph Node Status (%)				<0.001
Negative	2603(83.6)	1575(83.5)	261(44.3)	
Positive	510 (16.4)	311 (16.5)	328 (55.7)	

Table 2. Univariate analysis of the early-staged triple-negative breast cancer patients among three groups for overall and cancer-specific survival.

Characteristics	Number	Overall		Cancer-specific	
		5-year survival (%)	P-value	5-year survival (%)	P-value
Age			<0.001		0.044
<45 years	1006	89.4%		91.1%	
45–65 years	3034	90.6%		92.2%	
>65 years	1548	79.8%		89.7%	
Stage			<0.001		<0.001
I	2466	92.7%		96.1%	
II	3122	83.2%		87.6%	
Tumor size			<0.001		<0.001
<2 cm	2690	91.8%		95.4%	
2–10 cm	2888	83.4%		87.6%	
>10 cm	10				
Grade			0.012		0.019
Well differentiated	140	95.8%		98.3%	
Moderately differentiated	964	85.8%		92.0%	
Poorly differentiated	4461	87.4%		90.9%	
Undifferentiated	23	95.5%		95.5%	
Race			0.724		0.569
AI/AN	40	93.3%		93.3%	
Asian	516	91.9%		95.7%	
Black	1064	86.2%		90.4%	
White	3968	87.1%		91.1%	
Registry			0.146		0.288
Central	2118	85.9%		90.0%	
East	1290	88.3%		91.8%	
West	2180	88.4%		92.5%	
Lateral			0.013		0.002
Left	2704	88.9%		92.9%	
Right	2884	86.0%		89.9%	
Lymph nodes examined			<0.001		<0.001
<12	4804	88.4%		92.6%	
>=12	784	82.1%		85.1%	
Lymph nodes status			<0.001		<0.001
Negative	4439	89.5%		93.4%	
Positive	1149	79.7%		83.7%	
Chemotherapy			<0.001		0.278
Chemotherapy–	1273	80.6%		91.1%	
Chemotherapy+	4315	89.5%		91.4%	

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Characteristics	Number	Overall		Cancer-specific	
		5-year survival (%)	P-value	5-year survival (%)	P-value
Radiation			<0.001		<0.001
Radiation–	1886	82.7%		88.8%	
Radiation+	3702	89.8%		92.6%	
Surgery			<0.001		<0.001
BCS	3113	91.0%		94.0%	
Mastectomy	2475	82.9%		88.1%	
Group			<0.001		<0.001
BCS+RT	3113	91.0%		94.0%	
MRM	1886	82.7%		88.8%	
MRM+RT	589	83.7%		85.6%	

Table 3. Multivariate cox proportional model of early-staged triple-negative breast cancer patients among three groups for overall and cancer-specific survival.

Characteristics	Overall			Cancer-specific		
	HR	95% CI	P-value	HR	95% CI	P-value
Age						
<45 years	Ref			Ref		
45–65 years	1.297	0.939–1.793	0.115	1.352	0.945–1.936	0.099
>65 years	2.491	1.768–3.509	<0.001	1.954	1.305–2.925	0.001
Stage						
I	Ref			Ref		
II	1.339	0.901–1.991	0.149	1.375	0.842–2.245	0.202
Tumor Size						
<2 cm	Ref			Ref		
2–10 cm	2.035	1.447–2.861	<0.001	2.173	1.436–3.289	<0.001
>10 cm	11.396	2.656–48.892	0.001	8.582	1.110–66.339	0.039
Grade						
Well differentiated	Ref			Ref		
Moderately differentiated	5.588	1.366–22.858	0.017	5.604	0.767–40.939	0.089
Poorly differentiated	5.746	1.423–23.202	0.014	6.238	0.869–44.787	0.069
Undifferentiated	5.844	0.818–41.766	0.079	8.613	0.774–95.790	0.080
Race						
AI/AN	Ref			Ref		
Asian	1.016	0.239–4.315	0.983	0.655	0.149–2.883	0.576
Black	1.393	0.335–5.793	0.649	0.972	0.229–4.124	0.970
White	1.239	0.303–5.075	0.765	0.941	0.227–3.899	0.933
Registry						
Central	Ref			Ref		
East	0.791	0.597–1.050	0.104	0.797	0.567–1.120	0.191

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Characteristics	Overall			Cancer-specific		
	HR	95% CI	P-value	HR	95% CI	P-value
West	0.892	0.703–1.132	0.349	0.908	0.681–1.212	0.515
Lateral						
Left	Ref			Ref		
Right	1.306	1.064–1.603	0.011	1.481	1.152–1.906	0.002
Lymph nodes examined						
<12	Ref			Ref		
>=12	0.950	0.719–1.255	0.717	1.102	0.798–1.524	0.555
Lymph node status						
Negative	Ref			Ref		
Positive	2.065	1.566–2.740	<0.001	1.962	1.406–2.738	<0.001
Chemotherapy						
Chemotherapy–	Ref			Ref		
Chemotherapy+	0.448	0.349–0.575	<0.001	0.651	0.468–0.904	0.010
Group						
BCS+RT	Ref			Ref		
MRM	1.742	1.387–2.188	<0.001	1.876	1.415–2.489	<0.001
MRM+RT	1.449	1.038–2.204	0.029	1.701	1.168–2.478	0.006

3.2. BCS+RT demonstrated better prognosis than MRM and MRM+RT in early-staged triple-negative breast cancer patients

Both overall and cancer-specific survival analysis showed that BCS+RT had better prognostic effect than MRM and MRM+RT in the cohort of early-staged triple-negative breast cancer patients (overall survival, $P < 0.001$; cancer-specific survival, $P < 0.001$; Figure 1). We next conducted univariate cox proportional hazard analyses on all the clinical characteristics among three groups to explore their prognostic effect (Table 2). The overall 5-year survival of the patients was 91%, 82.7% and 83.7% in the BCS+RT, MRM and MRM+RT groups, respectively. Both the overall and cancer-specific survival showed differences among the three treatments. Older ages demonstrated poorer overall survival probability ($P = 0.043$), and patients in stage I had significantly better prognosis for both overall ($P = 0.008$) and cancer-specific probability ($P = 0.022$). In addition, smaller tumor sizes also tended to had a higher survival rate ($P = 0.044$). By taking all the risk factors into a multivariate cox proportional model (Table 3), MRM and MRM+RT remained to have detrimental effect on the prognosis compared with BCS+RT as shown by either overall (HR = 1.742, CI = 1.387–2.188, $P < 0.001$; HR = 1.449, CI = 1.038–2.204, $P = 0.029$) or cancer-specific survival (HR = 1.876, CI = 1.415–2.489, $P < 0.001$; HR = 1.701, CI = 1.168–2.478, $P = 0.006$). To rule out the differences of covariates existed among different treatment options (Table 1), we performed propensity score weighting and integrated the weights for each covariate in the multivariate cox proportional model (methods; Table 4). As a result, BCS+RT remained to be prognostic beneficial compared to the other treatment options ($P < 0.001$). Besides, stage II demonstrated a worse effect on both overall (HR = 2.104, CI = 1.672–2.649, $P < 0.001$) and cancer-

specific survival (HR = 1.805, CI = 1.369–2.381, $P < 0.001$) and chemotherapy had no statistical significance for cancer-specific survival (Table 4).

Table 4. Multivariate cox proportional model of early-staged triple-negative breast cancer patients among three groups for overall and cancer-specific survival (after PSW).

Characteristics	Overall			Cancer-specific		
	HR	95% CI	P-value	HR	95% CI	P-value
Age						
<45 years	Ref			Ref		
45–65 years	1.411	1.168–1.706	<0.001	1.509	1.226–1.858	<0.001
>65 years	3.267	2.683–3.979	<0.001	2.605	2.075–3.272	<0.001
Stage						
I	Ref			Ref		
II	2.104	1.672–2.649	<0.001	1.805	1.369–2.381	<0.001
Tumor Size						
<2 cm	Ref			Ref		
2–10 cm	1.764	1.456–2.137	<0.001	1.962	1.560–2.467	<0.001
>10 cm	9.746	4.004–23.719	<0.001	10.592	3.551–31.592	<0.001
Grade						
Well differentiated	Ref			Ref		
Moderately differentiated	8.215	2.605–25.912	<0.001	8.842	1.752–44.629	0.008
Poorly differentiated	9.305	2.966–29.190	<0.001	11.262	2.246–56.457	0.003
Undifferentiated	1.980	0.417–9.399	0.390	3.329	0.483–22.954	0.222
Race						
AI/AN	Ref			Ref		
Asian	0.666	0.312–1.421	0.293	0.521	0.241–1.126	0.097
Black	0.911	0.433–1.914	0.805	0.550	0.259–1.167	0.119
White	0.972	0.467–2.024	0.941	0.659	0.315–1.380	0.269
Registry						
Central	Ref			Ref		
East	1.050	0.904–1.221	0.521	1.199	1.010–1.422	0.038
West	0.829	0.723–0.952	0.008	0.755	0.637–0.894	0.001
Lateral						
Left	Ref			Ref		
Right	1.393	1.241–1.563	<0.001	1.768	1.535–2.037	<0.001

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Characteristics	Overall			Cancer-specific		
	HR	95% CI	P-value	HR	95% CI	P-value
Lymph nodes examined						
<12	Ref			Ref		
>=12	0.974	0.833–1.139	0.744	1.114	0.932–1.330	0.235
Lymph node status						
Negative	Ref			Ref		
Positive	1.727	1.484–2.010	<0.001	1.752	1.470–2.088	<0.001
Chemotherapy						
Chemotherapy–	Ref			Ref		
Chemotherapy+	0.639	0.555–0.736	<0.001	1.005	0.830–1.215	0.963
Group						
BCS+RT	Ref			Ref		
MRM	1.719	1.489–1.985	<0.001	1.832	1.534–2.189	<0.001
MRM+RT	1.356	1.165–1.578	<0.001	1.671	1.394–2.003	<0.001

4. Discussion

We analyzed 5,588 early-staged triple-negative breast cancer patients in the present study to compare the three treatments of BCS+RT, MRM only and MRM+RT. The results showed that BCS+RT demonstrated better prognosis than MRM only and MRM+RT treatments, indicating the safety of the choice of BCS+RT for early-staged TNBC patients.

Postoperative quality of life should be considered by clinicians for patients under the premise of selecting a safe treatment options, considering the fact that some patients underwent mastectomy will have many negative emotions such as depression, irritability, and lack of confidence postoperatively. Chemotherapy is widely used as an indispensable treatment for TNBC and it is written in the guidelines. According to our study, adjuvant radiotherapy can also significantly improve the prognosis of TNBC patients and BCS had better prognosis compared with MRM only, and MRM+RT for both overall and cancer-specific survival for early-staged TNBC patients. Thus, the comprehensive treatment of BCS combined with adjuvant chemotherapy and radiotherapy is recommended for the early-staged (stage I and stage II) TNBC patients.

Moreover, molecular markers should also be noticed and used to guide the treatment options with the concept of precision medicine. Among these markers reported in the previous studies, the mutation of BRCA1/2 and the status of PTEN are highly correlated with the occurrence and prognosis of triple-negative breast cancer[15,16].More investment should be obtained for the research of targeted drugs for treatment of TNBC patients[17]. In addition, immunotherapy has also shown its unique advantages for TNBC and should arouse more attention[18].

The surgical options for all molecular types of breast cancer are uniform in the NCCN guideline, and no special instructions are available for surgical options of triple-negative breast

cancer. Although many RCTs in different regions before had been done to explore which surgery has a better prognosis, no consensus has been reached on this issue. Hence, further research is needed to provide more tangible indications for the option of surgical method in the treatment of TNBC.

Abdulkarim et al. [9] once reported that the risk of locoregional recurrence (LRR) for women with early-staged triple-negative breast cancer treated with modified radical mastectomy without adjuvant radiation therapy was higher than that of breast-conserving surgery (BCS). However, as Adkins et al. [10] showed in the same year, BCS is not associated with increased LRR rates compared to mastectomy. A study from Van et al. indicated that BCS plus radiotherapy is at least equivalent to mastectomy with respect to overall survival taking some confounding variables into consideration [11]. Another study also found that some confounding variables such as age, lymphovascular invasion, grade, stage and the number of positive lymph nodes were all correlated to LRR for TNBC [12]. A recent study based on SEER database drew a conclusion that BCS plus radiotherapy had a better prognosis than mastectomy [13]. However, their conclusion might be biased due to several imbalanced conditions. One is the mismatched group comparison, radiotherapy was considered in the BCS group, but ignored in mastectomy group. The other is that confounding variables such as stage, grade and the number of positive lymph nodes which were also shown to be related to overall survival and cancer specific survival, had not been balanced in their research. Therefore, to make the results more reliable, propensity score weighting (PSW) was used in our study to correct these variables. To our knowledge, it is the first time that PSW was used to compare the efficacy among the three treatments (BCS+RT, MRM only and MRM+RT) for TNBC patients. Our study provided a theoretical basis for future explorations.

In spite of the rigorous design and analysis of the current study, it is only a case-control study based on database and prudence is needed when applying the result into practice. The conclusion needs to be verified by a large sample of multicenter RCT studies combined with long-term follow-up. At present, the surgical indications for TNBC have not been separately proposed. They are the same as all molecular types of breast cancer, including the result of margin evaluation, tumor size and the number of positive axillary lymph nodes [6]. Hence more precise guidelines need to be put forward to deal with different conditions of TNBC patients. In addition, it was reported that radiotherapy in different times have different effects on prognosis [14]. Further studies are needed to explore when to conduct radiotherapy that mostly benefit the TNBC patients.

In summary, our study suggested BCS+RT had better prognosis compared with MRM only, and MRM+RT for both overall and cancer-specific survival for early-staged TNBC patients. In other words, BCS+RT remained a safe choice for women who want to conserve their breasts without reducing therapeutic effects.

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Conflict of interest

The authors declare that they have no competing interests

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