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Comparative Study between Conservative Breast Surgery and Modified Radical Mastectomy in Triple Negative Cases

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ABSTRACT

Background: Breast cancer has a significant concern in modern researches due its mortality and associated psychological aspects.

Aim of the Work: The aim of this work is to compare conservative breast surgery (CBS) and modified radical mastectomy (MRM) regarding oncologic and cosmetic outcomes in women with primary breast cancer negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 triple-negative breast cancer (TNBC)**.**

Patients and Methods: This retrospective study included 20 patients presented by breast cancer. All patients underwent surgery at Al-Azhar University Hospitals. 10 patients were treated by conservative breast surgery and 10 patients were treated by modified radical mastectomy.

Results: We investigated Overall Survival in patients with TNBC treated with mastectomy compared with those receiving CBS. The analysis indicated that patients with CBS had better survival than patients with mastectomy in Overall Survival ($P < 0.001$).

Conclusion: patients with CBS exhibited improved in TNBC may be associated with the baseline characteristics between two groups. Most patients in the CBS group presented with better survival than did patients in the mastectomy group. CBS was favored over mastectomy.

Keywords: Breast cancer**,** Conservative breast surgery, Modified radical mastectomy.

INTRODUCTION

Breast cancer is the most common cancer in women throughout the world [(1)]. Breast conserving surgery and radiotherapy have been shown to provide similar local control and survival rates to radical procedures in the surgical treatment of early breast cancer [(2)]. In 1994, lumpectomy with simultaneous bilateral reduction mammoplasty were performed as a solution for cancer breast with macromastia and oncoplastic breast surgery was defined for the first time [(3)]**.**

Currently, patients with breast cancer are managed using clinical and histologic parameters, such as tumor size, lymph node (LN) status, and grade in conjunction with standardized immunohistochemical assessment of hormone receptors (ie, estrogen receptor [ER], progesterone receptor [PR]) and human epidermal growth factor receptor 2 (HER2) testing. Locoregional management of breast cancer has been implemented based on results of randomized controlled trials comparing CBS and MRM [(4)].

In these studies, locoregional outcome was not investigated with respect to molecular and/or biologic heterogeneity of breast cancer. Indeed, genomic and molecular profiling have paved the way to a paradigm shift toward new molecular classification with at least three major molecular subtypes [(5)] associated with differences in survival and response to treatment. To approximate these molecular subtypes, most studies are focused on biologic subtyping using ER, PR, and HER2 as biomarkers [(6)].

In particular, triple-negative breast cancers (TNBCs), which account for approximately 10% to 17% of all patients with breast cancer[(5)], present poorly differentiated tumors lacking expression of ER, PR, and HER2 on immunohistochemical analysis; they are characterized by a high proliferation rate and increased aggressiveness compared with other subtypes [(6)].

Because endocrine and HER2-targeted therapies cannot be offered, conventional cytotoxic chemotherapy followed by adjuvant RT is the standard of care for patients with TNBC. The paucity of therapeutic options emphasizes the urgent need to optimize the current locoregional management of patients with TNBC and reduce their risk of locoregional recurrence (LRR) [(7)].

AIM OF THE WORK

The aim of this study is to compare CBS with MRM regarding oncologic and cosmetic outcomes with primary breast cancer negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (triple-negative breast cancer [TNBC]).

PATIENTS AND METHODS

- **Study design**: prospective randomized comparative study which was approved by the Ethics Board of Al-Azhar University.
- **Study population**: breast cancer patients.
- **Patient's number**: 20 patients.
- **Study venue**: Al-Azhar University Hospitals.

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Inclusion criteria in the study:

- Patients with proven histopathology of early (stage I-II) breast cancer.
- Triple negative patients (Estrogen receptor, Progesterone receptor and Human epidermal growth factor receptor 2 HER2).
- No other lesions in the same or contralateral breast.

Exclusion criteria in the study:

- Patient with contraindication of CBS or radiation.
- Medically unfit for surgery.
- Patient with past history of breast cancer.

Patients were included if they agree to be included in the study and an informed consent was obtained.

Methods

All the twenty patients were subjected to the following:

1-Clinical data for every patient was recorded in a printed sheet:

A-History:

Personal history: Name, Age, Sex, Occupation, Residence and Special habits.

Present history: Analysis of complaint: Onset, Course. Risk factors.

Past history: Neurological, Cardiac, Operations, Drug intake, Hepatic disease, Lung disease, Similar conditions, Vascular procedure or Allergies.

- **Family history**

B-Examination:

I. **General examination:** Temperature, Respiration, Pulse, Weight, Head and neck, Heart and Abdomen.

Ethical approval:

The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Al-Azhar University.

Statistical Methods

All the collected data were coded on the computer and the statistical analysis was done using SPSS program (Statistical Package for Social Science).

RESULTS

The present study was conducted on 20 patients, 10 patients treated with MRM and 10 patients treated with CBS.

Their age ranged between 41-65 years in CBS group compared with 45-70 years with a mean age shown in (**Table 1**).

Table 1: Distribution of the studied patients regarding their age

	CBS	MRM	p-value
Age (Mean±S.D)	57.2±12.33	58.2±11.24	> 0.05

In CBS group 6 (60 %) of patients were married compared with 4 (40 %) in MRM group of patients. There was no statistically significant difference in this distribution.

In CBS group 6 (60 %) of patients were affected on the left side compared with 5 (50 %) in MRM group of patients. There was no statistically significant difference in this distribution.

In CBS group tumor size was **< 2 cm** in 6 (60 %) of patients w compared with 5 (50 %) in MRM group of patients. **(2-5) cm** in 4 (40%) and 4 (40%) in CBS and MRM groups respectively. One patient in MRM had **(> 5) cm** tumor size. Statistical correlation was found (**p-value: 0.047)**.

Table 2: Distribution of the studied patients regarding tumor size.

	CBS	MRM	p-value
T-size			
T1 (< 2)	6 (60%)	5 (50%)	**0.047**
T2 (2-5)	4 (40%)	4 (40%)	
T3 (> 5)	0 (0%)	1 (10%)	

In CBS group tumour size was **< 2 cm** in 6 (60 %) of patients w compared with 5 (50 %) in MRM group of patients. **(2-5) cm** in 4 (40%) and 4 (40%) in CBS and MRM groups respectively. One patient in MRM had **(> 5) cm** tumour size. This was statistically significant difference (**p-value: 0.047)**.

Table 3: Distribution of the studied patients regarding tumor stage.

	CBS	MRM	p-value
T-stage			
Tmic /T1a/T1b	2	2	**0.035**
T1c	5	6	
T2	3	2	

In CBS group tumor grade II was found in 3 (30 %) of patients compared with 2 (20 %) in MRM group of patients. Tumor grade III and IV was present in 7 (70%) and 8 (80%) in CBS and MRM groups respectively. This was statistically significant difference (**p-value: 0.001)**.

Table 4: Distribution of the studied patients regarding tumor grade.

	CBS	MRM	p-value
Grade			
I	0	0	**0.001**
II	3	2	
III and IV	7	8	

In CBS group, N 0 was presented in 7 (70 %) of patients compared with 8 (80 %) in MRM group of patients. N1 was in 3 (20%) and 2 (20%) in CBS and MRM groups respectively. N2 presented in only one patient in CBS group. This was statistically significant difference (**p-value: 0.022)**.

Table 5: Distribution of the studied patients regarding Lymph node involvement.

	CBS	MRM	p-value
Lymph node involvement			
N0	7	8	**0.022**
N1	2	2	
N2	1	0	

The hospital stays ranged from 1 to 3 days in CBS group and from 2 days to 4 days in MRM group.

In CBS group Locoregional recurrence occurred in 1 (10 %) of patients and 1 (10 %) in MRM group of patients. Distant metastases occurred in 1 (10 %) and 1 (10 %) in CBS and MRM groups respectively. Locoregional + Distant metastases occurred in only one patient in CBS group which was statistically non-significant (p-value: > 0.05).

Table 6: Distribution of the studied patients regarding relapse.

	CBS	MRM	p-value
Relapse			
Locoregional recurrence	1	1	> 0.05
Distant metastases	1	1	
Locoregional + Distant	1	0	

Wound healing time:

In CBS group wound healing time was 6.1 ± 2.34 days compared with 7.4 ± 3.36 in MRM group of patients. This was statistically non-significant (p-value: > 0.05).

Wound complications:

In CBS group seroma formation occurred in 1 (10%) of patients and 1 (10%) in MRM group of patients equally. Wound infection occurred in only one patient in MRM group of patients. Considering small sample size, this was statistically non-significant (p-value: > 0.05).

Table 2: Distribution of the studied patients regarding Wound complications

	CBS	MRM	p-value
Wound			
Seroma formation	1	1	> 0.05
Wound infection	0	1	

Comparison of survival between mastectomy and CBS

Overall Survival was investigated in patients with TNBC treated with mastectomy compared with those receiving CBS. Kaplan-Meier analysis was used to generate Overall Survival for these two surgical types (Figure).

The analysis indicated that patients with CBS had better survival than patients with mastectomy in Overall Survival (P < 0.001).

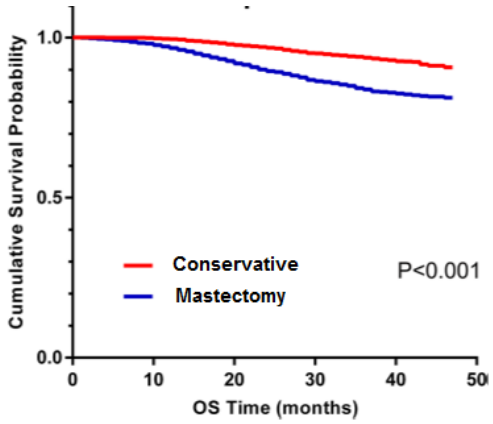

Figure 1: Comparison of survival between mastectomy and CBS

In the Multivariate analysis, excellent survival was identified in the CBS group when compared with the mastectomy group (HR, 0.579; 95%CI, 0.488 to 0.687; P < 0.001, for Overall Survival).

Table 3: Multivariate Cox proportional hazard regression model of overall survival (OS)

Variables	OS	
	HRs (95% CI)	***Pc***
Marital status		
Married	Reference	Reference
Not Married	1.308 (1.129–1.516)	< **0.001**
Grade		
I	0.263 (0.085–0.820)	***0.021***
II	**0.879 (0.707–1.093)**	**0.246**
III and IV	Reference	Reference
Lymph node involvement		
N0	Reference	Reference
N1	1.902 (1.540–2.349)	< **0.001**
N2	3.858 (2.527–5.889)	< **0.001**
Tumor Size (cm)		
T1 (< 2)	Reference	Reference
T2 (2-5)	1.534 (1.163–2.022)	**0.002**
T3 (> 5)	2.862 (2.069–3.958)	< **0.001**

DISCUSSION

According to SEER data to examine the different outcomes between CBS+RT and mastectomy for TNBC patients. The present study, showed that CBS+RT could improve B CSS and OS compared with mastectomy. Furthermore, upon stratifying the TNBC patients according to age, histology grade, stage, tumor size, and LN status, most patients with CBS+ radiotherapy (RT) presented with better survival than did patients with mastectomy, except for the grade I and stage I patients, who had the same survival in the CBS+RT and mastectomy groups. These findings indicated that CBS+RT is at least equivalent to mastectomy in terms of BCSS and OS. The finding that the long-term survival of early-stage breast cancer patients

treated with CBS+RT is at least equivalent to treatment with mastectomy has been demonstrated in several prospective and retrospective randomized controlled trials [7, 8, 9].

Recently, a Dutch population-based study conducted a comparison of 10-year OS and breast relative survival between CBS+RT and mastectomy for patients with early breast cancer (T1–2, N0–1, M0), which further confirmed the availability of CBS+RT [10]. However, these studies did not analyze the different outcomes between CBS+RT and mastectomy for TNBC patients. Furthermore, it was not observed that T1-2N0 TNBC treated with mastectomy without RT exhibited a significant increased risk of LRR compared with those treated with CBS until 2011 in a study from a cancer registry at a single institution [11].

Additionally, most studies on locoregional treatment of TNBC patients have been limited by relatively small sample sizes and have demonstrated inconsistent outcomes. **Nguyen *et al.*** identified a total of 1325 patients with TNBC who underwent CBS or mastectomy and found that the five-year LRR-free survival and distant metastasis-free survival rates were higher in the CBS group [12]. A cohort study including 1,138 Asian TNBC patients who were treated with CBS, mastectomy alone or mastectomy plus RT showed that for 775 T1-2N0-1M0 TNBC patients, the adjusted risks of mortality in the three groups were not significantly different [13]. However, their study consisted of 11,514 TNBC patients, constituting a larger cohort and a wide range of patients from the SEER database, and provided more convincing evidence that CBS+RT may not be contraindicated for TNBC patients. Additionally, the primary outcomes of BCSS and OS can represent the ultimate effects of different surgical types [14].

Our results showed that patients with CBS+RT exhibited improved OS in TNBC that may be associated with the baseline characteristics between the two groups and the application of RT in the CBS group. Considering baseline characteristics, we stratified the whole patient population according to age, grade, and T, and N stages, and most patients in the CBS+RT group presented with better survival than did patients in the mastectomy group, except for the grade I and stage I patients. Furthermore, we observed that 69.6% of patients underwent mastectomy without RT in our study. Thus, we suspected that the CBS+RT was favored over mastectomy may due to RT [15].

Accumulating evidence shows that radiation can induce an abscopal effect by stimulating the immune system to inhibit distant metastasis lesions. Additionally, we recognized that the BRCA1 mutation in TNBC patients might influence our results. A relevant study indicated that tumors lacking functional BRCA1 were highly radiosensitive [12]. Therefore, for TNBC patients, who share a considerable overlap in BRCA1 mutation, in the context of CBS + RT to the breast and surrounding tissue could eradicate recessive BRCA1- deficient tumor lesions and thereby decrease LRR [16]. However, to date, with no consistent evidence available, the significance of RT for CBS requires further exploration with large-scale prospective studies [17].

In the present work, there were 164 cases of 1003 tumors larger than 5 cm in size among TNBC patients accepting CBS+RT; those patients showed superior survival compared to those in the mastectomy group. This finding seemed discordant with the National Comprehensive Cancer Network (NCCN) guidelines that tumors larger than 5 cm in size are at high risk of recurrence for patients with CBS+RT. However, over the past several decades, neoadjuvant therapy (NAT) has proven beneficial for locally advanced breast cancer, as it renders inoperable tumors operable or downstages them, thus increasing the rates of CBS. In a large national database of 5,685 patients with T3 primary tumors, 15.6% of whom received CBS, similar survival rates were found for CBS and mastectomy. Furthermore, a study suggested that CBS with RT was significantly associated with a lower mortality risk than was mastectomy without RT for 363 T3-4, N2-3, M0 TNBC patients. Therefore, we speculated that CBS+RT could also be available after NAT in advanced TNBC patients, although information on NAT was absent from our study [18].

One of the strengths of the present study rests on the sizable number of triple-negative breast cancer patients in the SEER database, which ensures the strength and objectivity of our conclusions. Inevitably, our study had several limitations. In terms of follow-up data, it is a well-known fact that information regarding Her-2 expression in the SEER database was not available until 2010. Therefore, we were compelled to focus on the short-term survival outcomes after initial diagnosis and to identify any outcome-related factors; in this context, an inadequate follow-up duration may lead to skewed results. However, concerning TNBC subtype, the early peaks of recurrence and mortality occur within the first 2–3 years after diagnosis. Additionally, information on adjuvant or neoadjuvant chemotherapy not available for our study and probably unknown variables of tumor biology that we are still not aware of may exert a certain influence on our results [19].

In conclusion, from our study on SEER data, CBS+RT displayed elevated OS in TNBC patients compared to mastectomy, at least equally. Although cosmetic impairments resulting from mastectomy can

be addressed with immediate reconstruction, we still should consider the benefits of improved outcomes and an avoidable deterioration in quality life during the surgical decision-making process. Therefore, CBS+RT is a preferable choice for TNBC patients if given adequate adjuvant treatment [(18)].

CONCLUSION

Patients with CBS exhibited improved in TNBC which may be associated with the baseline characteristics between two groups. Most patients in the CBS group presented with better survival than did patients in the mastectomy group. CBS was favored over mastectomy.

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