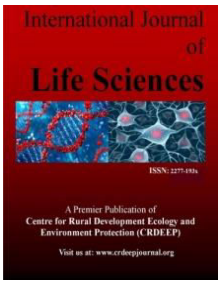
Vol. 8. No.4. 2019.

Contents available at:
www.crdeepjournal.org

International Journal of Life Sciences (ISSN: 2277-193x) SJIF: 5.79



Full Length Research Paper

Evaluation of Recurrence of Breast Cancer after Conservative Breast Surgery Compared with Modified Radical Mastectomy in Triple Negative Patients

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ARTICLE INFORMATION

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Article history:
Received: 20-09-2019
Accepted: 22-09-2019
Revised: 28-09-2019
Published: 01-10-2019

Key words:
Breast Cancer - Triple Negative Patients - Radical Mastectomy

ABSTRACT

Background: Breast cancer is the most common cancer in women throughout the world. 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. Aim of the Work: Compare CBS with 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). Patients and Methods: This retrospective study included 20 patients presented by breast cancer. All patients underwent surgery in El-Demerdash hospital, Military production specialized medical center, Al-Azhar university hospitals and El-monira general hospital. Results: In this study we compared between CBS and MRM in TNBC patients. It 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. 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. Conclusion: BCS 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, BCS is a preferable choice for TNBC patients if given adequate adjuvant treatment.

Introduction

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 [(1)]. 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 [(1)].

Locoregional management of breast cancer has been implemented based on results of randomized controlled trials comparing breast-conserving therapy BCT and modified radical mastectomy (MRM) [(2)].In those 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 associated with differences in survival and response to treatment [(3)]. To approximate these molecular subtypes, most studies have focused on biologic subtyping using ER, PR, and HER2 as biomarkers [(4)]. In particular, triple-negative breast cancers (TNBCs), which account for approximately 10% to 17% of all patients with breast cancer, present poorly differentiated tumors lacking expression of ER, PR, and HER2 on immunohistochemical analysis; they are characterized by a high proliferation rate [(5)] 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].

Several retrospective studies have used biologic subtype to assess risk of LRR in large populationof patients with breast cancer, which proportionally included small cohorts of patients with TNBC. Those studies showed an increased risk of LRR in patients with TNBC as compared with those with other biologic subtypes. However, they did not analyze risk of LRR based on initial locoregional management (ie, BCT *v* MRM) in patients with TNBC [8].

The aim of this study is to compare CBS with 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).

Patients and methods

This retrospective study included 20 patients presented by breast cancer. All patients underwent surgery in El-Demerdash hospital, Military production specialized medical center, Al-Azhar university hospitals and El-monira general hospital.

Inclusion criteria

Patients were included if matched the following criteria:

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

Exclusion criteria:

Patients were excluded if they had any of the following criteria:

- Patient with advanced breast cancer.
- Patents who are medically unfit for surgery.
- Patient with past history of breast cancer.
- Patients with contraindication of CBS or radiation.

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

Methodology

Each patient was subjected to the following:

1- Comprehensive medical history taking and careful clinical examination.

2- Laboratory investigations:

- Full Lab.: CBC, R.B.S, PT, PTT, INR, S. Urea, S. Creat., liver enzymes.

3- Imaging:

- Bilateral sonomammography.
- Plain chest-X-ray
- Pelvi- abdominal US.
- Bone scan.
- Further radiology wether local or systemic according to indication

4- Diagnostic pathology:

- Core biopsy or wedge biopsy.

5- Maximal surgical effort:

In CBS, the tumor with adequate safety margin as well as axillary L.Ns. were removed.

In MRM, the whole breast, pectoral fascia and axillary L.Ns. were removed.

Study design

- 10 patients were treated by conservative breast surgery.
- 10 patients were treated by modified radical mastectomy.

6- Post operative:

- *Cosmetic outcome:* follow up of patients during healing and after complete healing.
- *Post operative follow up:* after 6 months by U\S, sonomammography, or other radiology.
- Recurrence.

Statistical Analysis

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

- Description of quantitative variables as mean, SD and range.
- Description of qualitative variables as number and percentage.
- Chi-square test was used to compare qualitative variables.
- Two sample t-test was used to compare quantitative variables between independent groups in parametric data.
- Paired t-test was used to assess the statistical significance of the difference between two means measured twice for the same study group
- McNemar test was used assess the statistical significance of the difference between a qualitative variable measured twice for the same study group.
- P- value: level of significance
  - $P > 0.05$: Non significant (NS).
  - $P < 0.05$: Significant (S).
  - $P < 0.01$: Highly significant (HS).

Results

I- Demographic and Clinical Characteristics:

The present study was conducted on 20 patients, 10 patients treated with MRM and 10 ptients 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
Number of patients	10	10	
Age (Mean±S.D)	57.2±12.33	58.2±11.24	> 0.05
≤ 50	4 (40 %)	5 (50 %)	> 0.05
> 50	6 (60 %)	5 (50 %)	

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.

Table 2: Distribution of the studied patients regarding their marital status

	CBS	MRM	p-value
Marital status			
Married	6 (60 %)	4 (40 %)	> 0.05
Nor Married [a]	4 (40 %)	6 (60 %)	

a. Not married includes divorced, separated, single (never married), unmarried or domestic partner and widowed.

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.

Table 3: Distribution of the studied patients regarding side affected

	CBS	MRM	p-value
Laterality			
Left	6 (60 %)	5 (50 %)	> 0.05
Right	4 (40 %)	5 (50 %)	

II- Lesion characterization:

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 4: Distribution of the studied patients regarding tumour 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 5: Distribution of the studied patients regarding tumour stage

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

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

Table 6: Distribution of the studied patients regarding tumour grade

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

In CBS group N0 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 7: Distribution of the studied patients regarding Lymph node evolvement

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

III- Hospital stay:

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

Table 8: Distribution of the studied patients regarding Hospital stay

Hospital stay (days)	CBS	MRM
Range (days)	1 to 3	2 to 4

IV- Postoperative follow up:

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

Table 9: 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	

V- Wound status:

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).

Table 10: Distribution of the studied patients regarding Wound healing time

	CBS	MRM	p-value
Mean ± SD	6.1 ± 2.34	7.4 ± 3.36	> 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 11: Distribution of the studied patients regarding Wound complications

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

VI- Survival rate:

Comparison of survival between mastectomy and BCS

We investigated Overall Survival in patients with TNBC treated with mastectomy compared with those receiving BCS. Kaplan-Meier analysis was used to generate Overall Survival for these two surgical types (Figure 1). The analysis indicated that patients with BCS had better survival than patients with mastectomy in Overall Survival (P < 0.001). In the Multivariate analysis, excellent survival was identified in the BCS group when compared with the mastectomy group (HR, 0.579; 95%CI, 0.488 to 0.687; P < 0.001, for Overall Survival).

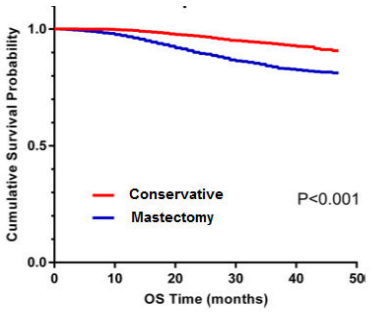

Fig 1: Comparison of survival between mastectomy and BCS.

Table 12: 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 envolvement	
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**

After multivariate adjustment, the differences between locoregional treatments in grade I (HR, 0.529; 95% CI, 0.032 to 8.626; P = 0.655, for OS) and stage I (HR, 0.737; 95% CI, 0.497 to 1.095; P = 0.131, for OS) was not significant (Table 13).

Table 13: Stratified according to clinical variables

Variables	BCS VS mastectomya	
	HRs (95% CI)	***Pc***
	Age at Diagnosis (y)	
20–49	0.756 (0.556–1.026)	0.073
50–79	0.492 (0.400–0.606)	**< 0.001**
	Histologic Grade	
I	0.529 (0.032–8.626)	0.655
II	0.558 (0.346–0.898)	**0.016**
III and IV	0.553 (0.460–0.666)	**< 0.001**
	T-stage	
Tmic/T1a/T1b	0.737 (0.497–1.095)	0.131
T1c	0.560 (0.443–0.708)	**< 0.001**
T2	0.483 (0.340–0.686)	**< 0.001**
	Tumor Size (cm)	
T1 (< 2)	0.690 (0.504–0.946)	**0.021**
T2 (2-5)	0.528 (0.420–0.664)	**< 0.001**
T3 (> 5)	0.525 (0.317–0.869)	**0.012**
	LN Status	
N0	0.626 (0.487–0.804)	**< 0.001**
N1	0.532 (0.389–0.727)	**< 0.001**
N2	0.536 (0.325–0.885)	**0.015**

Discussion

Breast cancer is the most common cancer in women throughout the world [9]. 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 [10]. In this study we compared between CBS and MRM in TNBC patients. It was conducted on 20 patients, 10 patients treated with MRM and 10 ptients treated with CBS. Their age ranged between 41-65 years in CBS group compared with 45-70 years. 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 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). A study found that patients with tumors larger than 5 cm in size among TNBC patients treated with BCS 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 BCS [11]. In accordance with this study, *Kaplan et al.* [12] reported that although patients with TNBC with T1N0 tumors are currently treated as a low-risk category with respect to LRR, they have greater risk of distant relapse than hormone receptor–positive/HER2-negative patients and should rather be treated with adjuvant chemotherapy. Interestingly, growing evidence from studies shows that TNBC subtype is associated with lower incidence of axillary LN involvement. Furthermore, recent studies have shown that tumor size is an unreliable predictor of LN metastasis [13].

The uncoupling between tumor size and LN status and increased risk of LRR for patients with TNBC treated with MRM compared with BCT suggest that these prognostic factors should not be considered as the only determinants of locoregional treatment decisions after MRM [14]. In CBS group tumour grade II was in 3 (30 %) of patients compared with 2 (20 %) in MRM group of patients. tumour grade III and IV was in 7 (70%) and 8 (80%) in CBS and MRM groups respectively. This was statistically significant difference (p-value: 0.001). In CBS group N0 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). Although some studies have suggested that T1-2N0 patients may benefit from adjuvant RT after MRM, this treatment is offered only to patients with LN-positive or T3N0 tumors. In our study, MRM was the only independent prognostic factor associated with increased risk of LRR in patients with T1-2N0 TNBC compared with BCT [15].

The hospital stay ranged from 1 to 3 days in CBS group and from 2 days to 4days in MRM group. In CBS group Locoregional recurrence occured in 1 (10 %) of patients and 1 (10 %) in MRM group of patients. Distant metastases occured in 1 (10 %) and 1 (10 %) in CBS and MRM groups respectively. Locoregional + Distant metastases occured in only one patient in CBS group. This was statistically non significant (p-value: > 0.05). As this study suggests, another study found that patients with T1-2N0 TNBC treated with MRM have worse outcome with significant increased risk of LRR compared with those treated with BCT. These findings should have direct implications for locoregional RT after MRM [16]. In *Brouckaert et al.* [16] study, an absolute reduction of LRR risk by 6% in T1-2N0 TNBC treated with BCT compared with MRM was found, there was no significant difference in OS between the BCT and MRM groups. Indeed, the Early Breast Cancer Trialists' Collaborative Group reported that reduction of 20% in risk of LRR at 5 years was associated with a 5.2% improvement in survival at 15 years [17]. 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). 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). We investigated Overall Survival in patients with TNBC treated with mastectomy compared with those receiving BCS. Kaplan-Meier analysis was used to generate Overall Survival for these two surgical types. The analysis indicated that

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

After multivariate adjustment, the differences between locoregional treatments in grade I (HR, 0.529; 95% CI, 0.032 to 8.626; P = 0.655, for OS) and stage I (HR, 0.737; 95% CI, 0.497 to 1.095; P = 0.131, for OS) was not significant. The finding that the long-term survival of early-stage breast cancer patients treated with BCS is at least equivalent to treatment with mastectomy has been demonstrated in several prospective and retrospective randomized controlled trials [11]. Recently, a Dutch population-based study conducted a comparison of 10-year OS and breast relative survival between BCS and mastectomy for patients with early breast cancer (T1–2, N0–1, M0), which further confirmed the availability of BCS [18]. However, these studies did not analyze the different outcomes between BCS 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 BCS until 2011 in a study from a cancer registry at a single institution [19]. Additionally, most studies on locoregional treatment of TNBC patients have been limited by relatively small sample sizes and have demonstrated inconsistent outcomes. *Adkins et al.* [20] identified a total of 1325 patients with TNBC who underwent BCS or mastectomy and found that the five-year LRR-free survival and distant metastasis-free survival rates were higher in the BCS group.

A cohort study including 1,138 Asian TNBC patients who were treated with BCS, 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 [21]. Our study had several limitations. In terms of sample size, follow-up data, it is a well-known fact that documentation is not accurate in our institutions and non compliance of our patients. Therefore, we were compelled to focus on the short-term survival outcomes after initial diagnosis and to identify any outcome-related factors.

Conclusion

In conclusion, BCS 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, BCS is a preferable choice for TNBC patients if given adequate adjuvant treatment.

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