Is triple-negative breast cancer a justification for mastectomy or breast conservative surgery? An institutional experience.

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Abstract

Background: the debate of breast conservative surgery (BCS) and modified radical mastectomy (MRM) is not over in triple-negative breast cancer (TNBC), so we aimed to highlight the differences in recurrence rates, disease-free survival, and overall survival in the two major surgical procedures of BCS and MRM among a retrospective cohort of TNBC patients.

Patients and methods: 73 women with TNBC (ER-ve, PR-ve, HER2 neu-ve) were collected from patients' data registry system from the beginning of 2011 to the end of 2012, and then their files were reviewed for different clinical, pathological, surgical procedures, neoadjuvant and adjuvant treatment, and response criteria, also, different patterns of failures, prognostic factors, whenever available, and survivals.

Results: 54.8% (40 patients) of women underwent MRM while 45.2% (33 patients) of women only underwent BCS, more local recurrences were gained in those women with BCS than MRM (P=0.038) without significant difference in the time to local recurrence among both groups (P=0.4), also no significant differences in disease-free survival P=0.1, but overall survival was significantly better for BCS compared to MRM (P=0.007).

Conclusion: We found that more local recurrences were developed in the BCS group than the MRM group but the BCS group had significantly better OS than the MRM group. So, it is too early to conclude that MRM is the standard of care for TNBC, and further large multicentric studies are needed to disclose this debate

Key words: triple-negative breast cancer; breast conservative surgery; modified radical mastectomy; recurrence; disease-free survival; overall survival.

Introduction:

Worldwide, over 2 million new cases of breast cancer were registered in 2018, although Egypt was not one of the 25 top countries in breast cancer as a result of lacking incidence registry at the national level in Egypt, breast cancer takes in the lion's share to represent about 25% of all cancers (1).

Triple-negative breast cancer (TNBC) is a specific subset of breast cancer with aggressive clinical behavior and poor prognosis (2). It represents about 15-20% of all breast cancer types, commonly; it progresses within 3-5 years to end the lives of women earlier than any other type of breast cancer.

Recently, using nCounter Gene Expression Codesets, TNBC was classified into subtypes including basal-like immune-activated (BLIA), basal-like immune-suppressed (BLIS), luminal androgen receptor (LAR), and mesenchymal (MES) subtype (3) to justify the heterogeneity of treatment outcomes in this type of breast cancer.

Given that, it is an aggressive disease with a higher risk of locoregional failure, also higher incidence of chemoresistance to the traditional anthracyclines and taxanes chemotherapy (4, 5) with the absence of effective targeted treatments, these scenarios increase the concerns of potential inadequacy of BCS in those patients with the potential of decreasing the possibility of local failure by mastectomy. Also, the absence of RT following mastectomy in early T1-T2 N0 breast cancer raises a question to intensify the treatment by RT in TNBC and minimize the local failure (6-10).

The 5-year loco-regional recurrence-free, disease-free, and overall survival were significantly higher in T1-T2 N1 TNBC patients who underwent BCS and RT

compared with mastectomy (p=0.01, 0.006, 0.005 respectively) in a pooled analysis of two multicenter retrospective studies (11), while in another study, it was associated with worse survival (12).

Yet, the debate of BCS and MRM is not over, therefore, this study aimed to highlight the differences in recurrence rates, disease-free survival, and overall survival in the two major surgical procedures of BCS and MRM among a retrospective cohort of TNBC patients.

Patients and Methods:

This study was a retrospective cohort one which involved 73 women with TNBC, T1-T4, N0-N3, and M0, treated surgically with either BCS (lumpectomy + negative margins and axillary evacuation) (Fig.1) or MRM at Surgical Oncology Department, South Egypt Cancer Institute, Assiut University. Neoadjuvant chemotherapy for cytoreduction was allowed and adjuvant chemotherapy was followed according to standardized guidelines, also, all females included within the BCS group received adjuvant RT to minimize the risk of loco-regional recurrence, while those in the MRM group received adjuvant RT whenever indicated. Neoadjuvant and adjuvant treatment was given at Clinical Oncology Department of Assiut University Hospital, Assiut University, and Medical Oncology Department, South Egypt Cancer Institute, Assiut University. The study was approved by the Institutional Review Board of faculty of medicine (IRB no=17300416), the procedures followed were following the ethical standards of our institutional committee on human experimentation and with the Helsinki Declaration of 1975 and revised in 2000.

Figure (1): Inverted T mammoplasty

Data collection:

73 women with TNBC (ER-ve, PR-ve, and HER2 neu-ve) were collected from patients' data registry system, and then their files were reviewed for different clinical, pathological, surgical procedures, neoadjuvant and adjuvant treatment, and response criteria, also, different patterns of failures, prognostic factors, whenever available, and survivals.

The study involved these patients from the beginning of 2011 to the end of 2012, and then all patients were followed up from the date of diagnosis till the date of death or last follow up registered in their files for a range from 15-100 months (median follow up period = 40 months, during this period, patients were followed up periodically every 3 months by clinical examination, breast sonomammography, chest x-ray, and abdominal ultrasound, and every 6 months by multislice ct scan (MSCT) of the chest and pelvi-abdomen ± bone scan or PET-CT if needed for 5-years, and yearly thereafter.

Endpoints:

The primary endpoints for this study were recurrence rates for both groups (TNBC patients with BCS and MRM), time to local recurrence, and disease-free survival (DFS).

Secondary endpoints were overall survival (OS), distant recurrence rates, and clinical characteristics.

Statistical analysis:

Statistical package for social sciences (SPSS) version 20 was used for data analysis. All quantitative data were expressed as mean ± standard deviation (SD). Differences in the mean between different groups of subjects were calculated using the independent sample t-test, and one way ANOVA, while Chi-square test to find a significance for different qualitative variables, Kaplan-Meier test was used to graph the survival curves and log-rank test to find a difference between BCS and MRM groups, p-value <0.05 was considered significant, disease-free survival (DFS) was calculated from the time of diagnosis to time of recurrences or death, and overall survival (OS) was calculated from the time of diagnosis to time of death or last follow up.

Results:

The characteristics of 73 female patients with TNBC were provided in (Table.1), where 76.8% of them had T1-T2, and 71.2% of women also had N0-N1(most of our patients were early breast cancer), also, 94.5% of these women had IDC, and 65.8% of women had less than 25% DCIS.

Surgical procedures:

54.8% (40 patients) women underwent MRM while 45.2% (33 patients) women underwent BCS (Fig.2).

Table (1): Characteristics of 73 women with TNBC

characteristics	N (%)
Age (mean ±SD)	49.4±1.3
Median	50 years
Range	28-77
Side	
Rt	32 (43.8%)
Lt	41 (56.2%)
T stage	
T1	8 (11%)
T2	48 (65.8%)
T3	16 (21.9%)
T4	1 (1.4%)
N stage	
N0	27 (37%)
N1	25 (34.2%)
N2	13 (17.8%)
N3	8 (11%)
Pathologic subtype	
IDC	69 (94.5%)
ILC	4 (5.5%)
Pathologic grade	
G1	2 (2.7%)
G2	53 (72.6%)
G3	18 (24.7%)
DCIS*	
<25%	48 (65.8%)
≥25%	25 (34.2%)
positive LVI	31 (42.5%)
local recurrence	22 (30.1%)
distant metastases	27 (37%)

Data expressed as mean ±SD, number, percentages, IDC; invasive ductal carcinoma, ILC; invasive lobular carcinoma, DCIS; ductal carcinoma in situ, LVI; lymphovascular invasion; *according to National Comprehensive Cancer Network (NCCN) Version 5,2020.

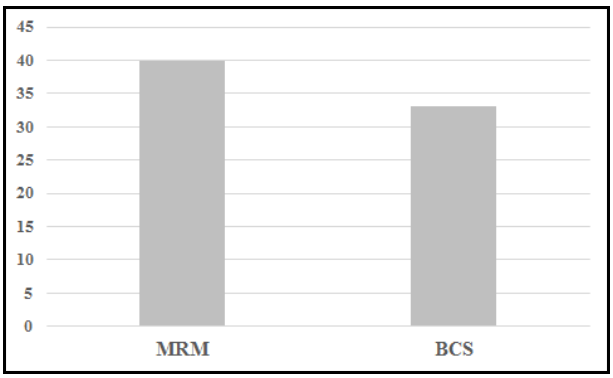

Figure (2): Types of surgery for 73 females with TNBC

No significant differences in T stage (p=0.06), pathologic types (p= 0.8), DCIS (p=0.52), LVI (p=0.3), side (p=0.23), and the number of positive lymph nodes (p=0.6) between women with BCS and MRM, while there was a significant difference between both groups in N staging (p=0.01), (Fig.3).

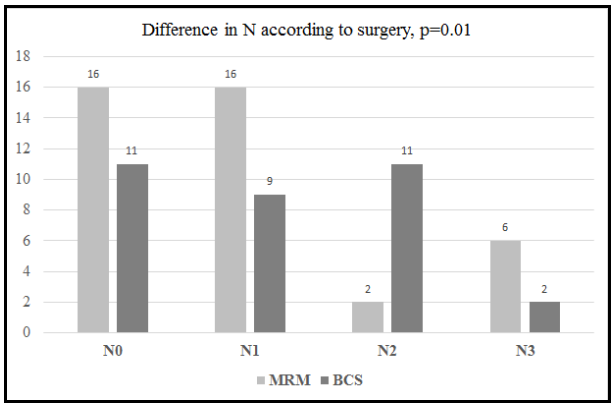

Figure (3): Differences in N stage among females with BCS and MRM, Chi-square test.

Local recurrence

Our results confirmed that more local recurrences were observed in those women with BCS than MRM (p=0.038), (Fig.4), although, 45.2% of patients with BCS developed local recurrences compared with 20% in the MRM group but no significant difference in the time to local recurrences among both groups with meantime for local recurrence was 29.75±3.1 months in MRM group (median = 29 months) and 25.571±4.98 months (median=25 months) for BCS group (p=0.4), (Fig.5).

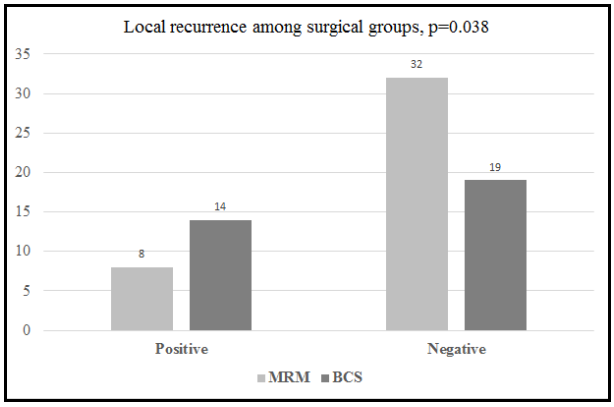

Figure (4): Differences in local recurrences among MRM and BCS groups, Chi-square test.

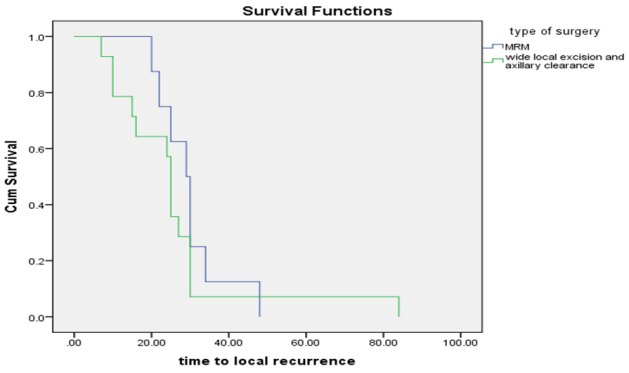

Figure (5): Showed the time to local recurrence for both groups with no significant difference, Log-rank=0.723, *p*=0.4

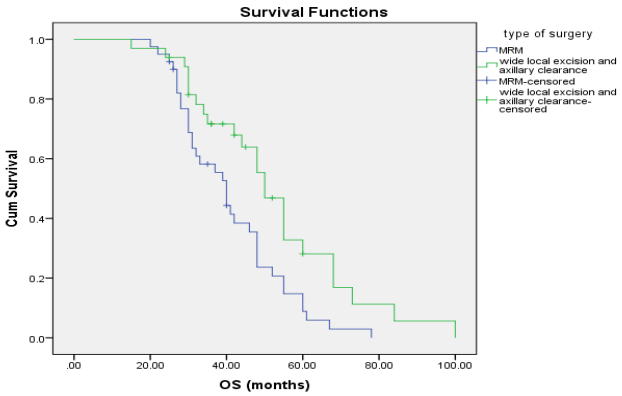

Figure (7): Showed a significant difference in the mean OS between both groups, *p*=0.007

Also, no significant difference in distant metastatic rates among both groups (MRM=13/40 vs. BCS=14/33, *p*=0.4). Furthermore, no significant differences in the time to distant metastasis (mean time for MRM=27.23±3 vs. 28.57±5.3 for BCS, *p*=0.5).

DFS and OS among both groups

No significant difference in DFS between the two groups. The mean DFS for the MRM group was 36.7±2.5 months with 95% CI =31.9-41.5, while that of the BCS group was 43.8±4.6 months with 95% CI=34.8-52.8, Log Rank=2.19, *p*=0.1, (Fig.6).

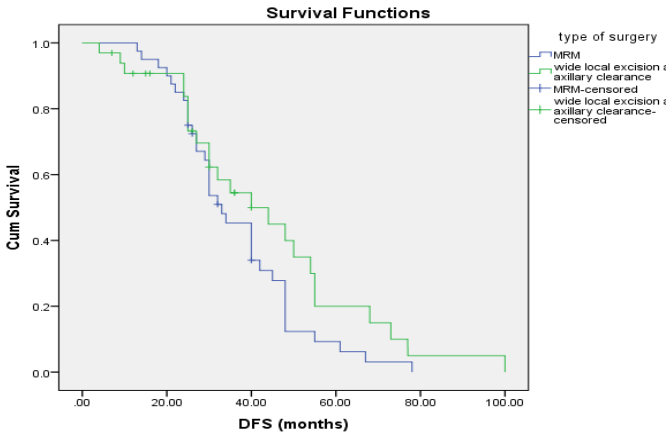

Figure (6): Showed no significant differences in DFS of both groups, *p*=0.1

The mean OS is significantly more in the BCS group compared to the MRM group. The mean OS for the MRM group was 41.05±2.31 with 95% CI=36.5-45.57 months, while for BCS, it was 52.5±4.05 with 95% CI=44.6-60.5, Log Rank=7.3, *p*=0.007, (Fig.7).

5-year DFS for the whole study patients was 9.6%, while 5-year OS was 16.4%. 3-year DFS for those with MRM was 40%, while for those with BCS was 42.4%, and 3-year OS was 47.5% for the former group and that of the latter group was 39.3%, additionally, the results were not significant (*p*=0.8, *p*=0.5 respectively)

Discussion:

Generally, in absence of effective targeted therapy, TNBC patients are at high risk for locoregional recurrences (2), several studies have proved the survival advantage of breast conservative surgery over mastectomy (13-16), without considering different molecular subtypes.

Our results demonstrated insignificantly better DFS for BCS over MRM, while significantly better OS for the former group than later one (P=0.007), higher local recurrence rates occurred in those with BCS over MRM (P=0.038), but no significant differences in time to local recurrence, distant metastatic rate, and time to distant metastasis.

Currently, there is a great concern considering MRM for those patients with more aggressive features in TNBC including higher grade, perineural invasion, increased number of positive LNs, and high DCIS, in spite, loco-regional recurrences are higher among those who underwent BCS (17), despite the loco-regional controls among TNBC patients with breast conservative surgery (BCS) followed by radiotherapy (RT), and modified radical mastectomy (MRM) were clarified to be comparable in a recent meta-analysis (18).

A recent study with univariate and multivariate analyses of different prognostic features for 5-year local recurrence-free survival (LR-RFS), 5-year DFS, and 5-year OS showed significantly higher results for BCS and RT over mastectomy (11) but more patients developed local and regional recurrences with BCS, our results agreed with the previous study regarding the mean OS which was significantly better for the BCS group than the MRM group.

Regarding the issue of loco-regional recurrences, a meta-analysis by Wang et al. revealed that BCS+RT was less likely to develop loco-regional recurrence

when compared with mastectomy, but comparisons according to the specific stage were not performed (18). These results were contradictory to ours.

More recently, Abdulkarim et al. (8) showed that BCS+RT led to a higher locoregional control as compared with mastectomy in pT1-2N0 TNBC, even as a comparable loco-regional control between the two groups was shown in a similar population from Memorial Sloan Kettering (19).

About 62% of ipsilateral breast recurrences are commonly true recurrences (20) with 76% 5-year OS, and according to Fisher et al. these true recurrences were defined as secondary tumors located in the same quadrant or within 3 cm from the previous primary site (21), in our study, we followed the definition of St. Gallen which involved recurrences developed in the same quadrant and of the similar molecular phenotype (22).

In a previous study, BCS patients with luminal B, HER2-positive phenotype, and triple-negative subtypes had higher recurrence rates than luminal A subtype without considering the type of these recurrences whether true or new primaries (23), this study indirectly pointed to our results highlighting that TNBC patients might have high recurrence rate after BCS.

Dauren et al. (24) demonstrated that 30% of TNBC phenotype had true recurrences following BCS; with a short time for relapse (median time was 37 months), however, our results showed that 42.5%% of TNBC patients had local recurrence after BCS compared to 20% following mastectomy with median time for recurrence of 29 months for the former and 25 months for the later (P=0.4).

Lan Mu et al (25), investigated in a cohort of 757 patients with early breast cancer treated surgically with BCS, the risk of locoregional relapse, distant metastases, total relapses and mortality associated with different molecular subtypes and found that TNBC was associated with 5-year loco-regional recurrence rate of 7.3% and 5-year mortality rate of 4.7% significantly higher than luminal subtypes without significant differences in distant metastatic rate and total relapses, but after multivariate analysis, TNBC patients were not at significantly increased 5-year risks of loco-regional recurrence, distant metastasis, total relapse or mortality rates sufficiently to be considered appropriate candidates for BCS, however, in our results we did not take into consideration other molecular subtypes and we emphasized on TNBC as it is an aggressive disease especially in Egypt with a 5-year DFS of 71% and a 5-year OS of 88% with a relapse rate of 21.8% (12/55) in a recent study (26), while in our results 5-year DFS was 9.6%, 5-year OS was 16.4%, and the local relapse rate was 30.14% (22/73).

Furthermore, in accordance with our results, Solin et al (27) compared 90 TNBC patients to 429 non-TNBC patients regarding the point of local recurrence and detected a significantly higher recurrence rate for TNBC versus non-TNBC in univariate analysis (8% vs. 4%, P=0.041).

Despite more local recurrences developed in the BCS group but it is difficult to reach a solid conclusion because of the small number of patients included in groups, heterogeneity of patients, retrospective nature of the study, potential selection/confounding bias, and absence of stage-to-stage comparisons.

In conclusion, we found that more local recurrences were developed in the BCS group than the MRM group but the BCS group had significantly better OS than the MRM group. So, it is too early to conclude that MRM is the standard of care for TNBC, and further large multicentric studies are needed to disclose this debate.

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Contributions of authors:

Hussein Fakhry was the surgeon responsible for performing BCS and MRM done for all patients, data collection and follow up of patients; Asmaa M. Zahran was responsible for conception and design; Hebat Allah Mahmoud was responsible for the acquisition of data, and Amal Rayan was responsible for analysis, interpretation of data, and drafting of the manuscript and all authors participated in final revision of the manuscript before submission.

Conflict of interest: all authors declared that they had no conflict of interest.

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Data availability statement: all data generated or analyzed during this study are included in this submitted article.

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