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Feasibility of Breast Conserving Surgery in Stage IIIA Breast Carcinoma Patients in the Absence of Neoadjuvant Therapy

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Abstract

Background: Preoperative determination of the extent of viable residual tumor is an important issue after neoadjuvant treatment. On the other hand, retrospective data suggest that breast-conserving surgery is feasible up to stage IIIA breast cancer without preoperative therapy.

Methods: We retrospectively analyzed 164 patients who underwent breast-conserving surgery followed by adjuvant chemotherapy and/or endocrinal therapy with whole breast radiation between 2005 and 2012. Of those, 116 patients had stages I and II (group 1) breast cancer, whereas 48 patients had stage IIIA (group 2).

Results: After a median follow-up of 40.4 months, 18 (15.5%) patients in group-1and 8 (16.6%) in group-2 developed ipsilateral breast tumor recurrence (P=0.77). Mean time to tumor recurrence was 19 months in group 1 and 17 months in group 2 (P=0.5). However we found more ipsilateral breast tumor recurrence in hormone negative tumors (P=0.002), high grade tumors (P=0.021), young age (P=0.017) and lymph node positive cases (P=0.011). We observed no significant difference between N1 and N2 lymph node status (P=0.241).

Conclusion: Our data suggest that breast-conserving surgery with R0 resection is feasible in stage IIIA cases whenever cosmetic appearance can be maintained as long as surgery will be followed by radiotherapy and chemotherapy. A prospective study with larger numbers is recommended for further evaluation of this issue.

Keywords: BCS, Stage IIIA, Tumor size, Neoadjuvant chemotherapy

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Introduction

Breast-conserving surgery (BCS) is a possible option for early-stage breast cancer. Long-term follow-up in many studies have reported comparable disease-free and overall survival rates between mastectomy and BCS.[1,2] Neoadjuvant therapy in the form of chemotherapy or endocrine therapy followed by

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surgery is a popular option as a multidisciplinary approach for operable breast cancer (OBC). The potential advantages of this approach include tumor down staging, increasing the rates of breast conservation and the possibility of monitoring tumor response.[3] However, randomized studies indicate that the survival benefits from neoadjuvant and adjuvant of particular systemic treatments are similar.[4] In addition, the biggest barrier to the use of BCS after neoadjuvant treatment remains the inability to determine the extent of viable residual tumor preoperatively, particularly when cancer dies in a honeycomb or buckshot-type pattern. Consequently, the need for accurate assessment of neoadjuvant treatment response is a main issue. MRI appears to be the most reliable method to assess both the extent of residual disease and the pattern of response, but it may overestimate the extent of residual disease and sometimes fail to identify microscopic islands of viable residual tumor.[5,6] MRI is expensive and not widely used in most centers, particularly in developing countries. Therefore, the volume of breast tissue which needs to be excised during BCS is usually estimated by palpation, which leads to increased positive resection margins in up to 41% of patients in palpation-guided surgery.[7-9]

The use of BCS is usually questionable for large tumor size, as it has long been considered as a contraindication; some guidelines recommend the use of neoadjuvant treatment for large tumors.[10] However, a higher T-status according to the TNM system may not be an absolute contraindication for BCS as long as surgical margins are properly maintained and postoperative radiotherapy (RT) is enabled.[11] Some studies suggest that the size of the tumor does not impact the oncologic outcome after BCS when compared with mastectomy in patients with breast cancer who have tumor sizes up to 5 cm.[1, 12] This has been confirmed by another study which focused on large tumor size and suggested the use of BCS in patients with pT3 or pT4 breast cancer regardless of neoadjuvant chemotherapy.[13]

In addition the use of neoadjuvant treatment in clinical practice is sometimes faced with problems, particularly in Egypt as most patients prefer rapid removal of their tumor because the delay in surgical approach can be a cause for anxiety. Clinicians usually prefer surgery followed by adjuvant therapy.[14]

We conducted this study to assess the feasibility of BCS without neoadjuvant treatment in clinically operable stage IIIA breast cancer.

Materials and Methods

Patient selection

We retrospectively reviewed the files from 164 patients diagnosed with invasive ductal carcinoma who underwent breast conserving surgery followed by adjuvant chemotherapy and/or endocrine therapy with whole breast radiation from January 2005 to December 31, 2012 at South Egypt Cancer Institute, Assiut University, Egypt. Patients with stages I-IIIA were included and stratified according to tumor stage into two groups. Group-1 included 116 patients with stages I and II cancer, whereas group-2 included 48 patients with stage IIIA cancer. Patients with prior malignancy, synchronous bilateral breast cancer and those with positive surgical margins were excluded from the study.

The study was approved by the local Institutional Review Board Committee and conducted in accordance with the Declaration of Helsinki.

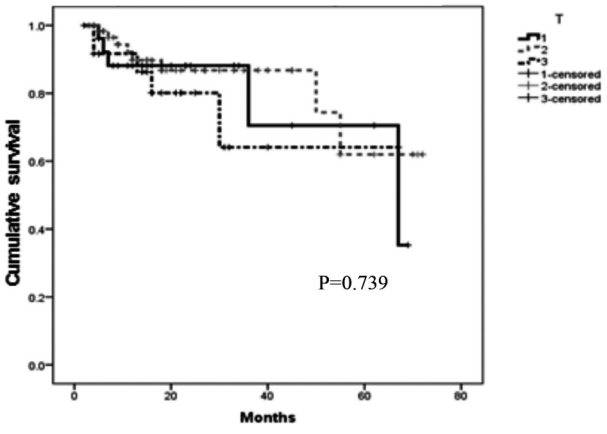

Figure 1. Ipsilateral local recurrences free survival regarding different tumor size

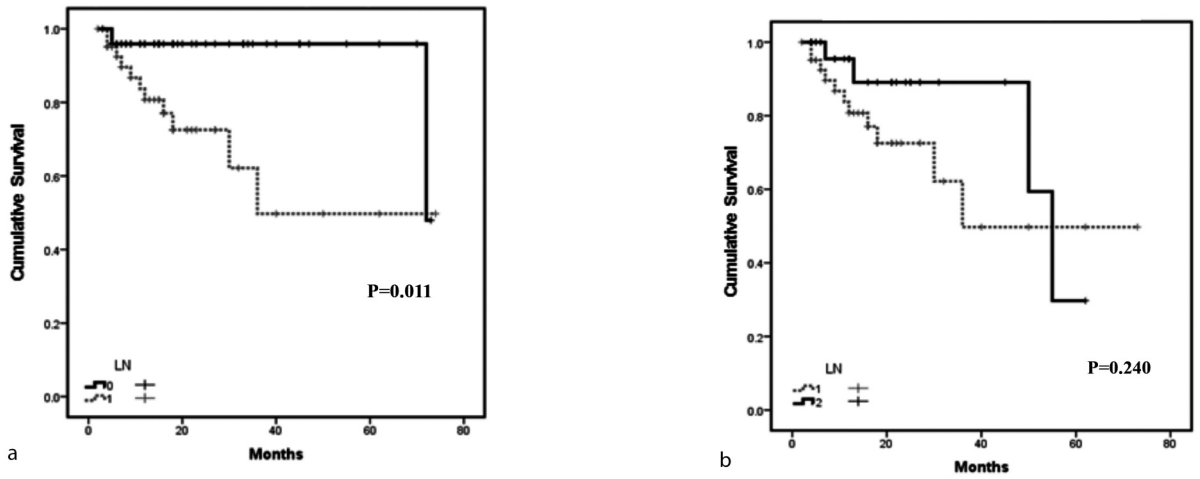

Figure 2. Ipsilateral lateral local recurrence free survival regarding lymph node status; a) between N0 and N1, b) N1and N2.

Study procedures

In each group we analyzed patients' characteristics of age, menopausal status, tumor size, lymph node status, nuclear grade, disease stage, hormone status, Her2/neu status (when data was available) and type of adjuvant chemotherapy. The disease was staged according to the 2010 TNM Staging for Breast Cancer (AJCC) system.[15]

Treatment

Surgery

All patients underwent local excision of the primary breast tumor with a 2 cm safety margin and ipsilateral levels I and II axillary lymph node excision.

Systemic therapy

Both Taxane-based (Adramycin Cyclophosphamide -Taxel (AC-T)) and anthracyline-based (5-Fluorouracil Epirubicin Cyclophosphamide (FEC) or Cyclophosphamide Adriamycin Cyclophosphamide (FAC)) were used as adjuvant chemotherapy treatments. None of the patients received adjuvant trastuzumab. Adjuvant endocrine therapy was used for all hormone positive patients. Premenopausal patients received Tamoxifen and postmenopausal patients took an aromatase inhibitor.

Postoperative radiation therapy (RT)

All patients received external beam RT to the whole breast. The RT dose was 50 Gy administered in 2 Gy daily fractions to the breast and chest wall. We used 3-D planning by two parallel opposed tangential fields with 6 MV photon beams. Supra-clavicular irradiation (50 Gy/25 fractions/5 weeks) was given only to patients who had positive axillary lymph nodes. In addition, all patients received a boost dose of 16 Gy administered in 8 fractions to the tumor site using 12 MeV electrons.

Follow-up

All patients were followed every 4 to 6 weeks after completion of RT, then every 3 months thereafter with yearly breast imaging studies. Follow-up time was counted from date of diagnosis to the date of the first event, or to the last known confirmed date of breast cancer disease-free status. In total, 15 (8%) patients were lost to

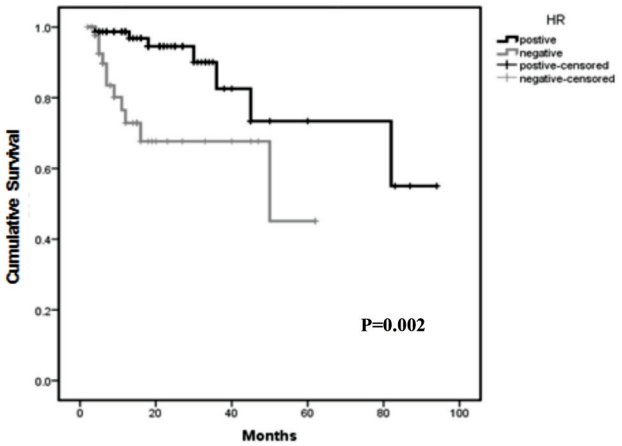

Figure 3. Ipsilateral local recurrence free survival regarding hormonal status

Table 1. Patients' characteristics.

Parameter	Stages I & II			Stage III(A)			*P*-value
	N= 116		%	N=48		%	
Age (24-70 years)							
<40	41		35	18		37.5	NS
>40	75		65	30		62.5	
Menopausal status							
Premenopausal	68		58.6	28		58.3	NS
Postmenopausal	48		41.3	20		41.6	
Stage	**Stage I**	17	14.6	**Stage IIIA**	48		
	Stage IIA	54	46.5	T3N1 M0	14	29	
	Stage IIB	45	38.7	T1 N2 M0	8	16.6	
				T2 N2 M0	15	31.2	
				T3 N2 M0	11	22.9	
Tumor size (T)							
T1	35		30	8		16.6	
T2	69		59.4	15		31	
T3	12		10.3	25		52	
Lymph node (N)							
N0	74		63	0		0	
N1	42		36.2	17		34.9	
N2				31		61.9	
Chemotherapy adjuvant							
Taxane-based	25		21.5	16		33.3	0.001
Anthracycline-based	83		71.5	32		66.5	0.045
None	8		6.8	0		0	
Hormone receptor (HR) status							
(+)	72		62	32		63.5	0.943
(-)	44		38	16		36.5	0.785
Her2/neu status	N=46			N=21			
(+)	12		26	7		33	0.057
(-)	34		73	14		66	0.064
HR (+ve) & Her2/neu (+ve)	7		15.2	4		19	0.073
HR (+ve) & Her2/neu (-ve)	24		52	9		42.8	0.057
HR (–ve) & Her2/neu(+ve)	5		10.8	3		14.2	0.050
Triple (–ve)	10		21.7	5		23.8	0.064
Grade (low)	8		6.8	2		1.5	
Grade (intermediate)	75		7.2	25		65	0.001
Grade (high)	23		20	21		33.5	

N: Number, T: Tumor size, N: Lymph node

follow-up.

Study endpoints

Ipsilateral breast tumor recurrence (IBTR) was the primary endpoint in this study. We calculated recurrence from the date of IBTR diagnosis. All patients had yearly breast imaging studies. For each recurrence, imaging of the primary and recurrent tumor was reviewed in the light of pathology reports and operative notes in order to better characterize location of the recurrent tumor with respect to the excision site and scars. For each case, mammograms and ultrasounds were reviewed. Each IBTR was defined as recurrence in the same quadrant of the breast and within three centimeters of the primary tumor bed.

Cosmetic appearance was the secondary end point. This end point was assessed after surgery by inquiring about the level of patient satisfaction. Patients selected one of three answers (excellent, good or bad) regarding cosmetic appearance.

Statistical analysis

Variables were summarized using descriptive

Table 2. Factors that affect ipsilateral tumor recurrence.

	Multivariate analysis		
Factor	***P*-value**	**HR**	**5% CI**
Age	0.017	5.387	1.512-19.523
Tumor size	0.739	1.125	0.568-2.247
Hormone +/-	0.002	4.769	1.780-12.776
LN +/-	0.011	5.280	1.464-19.048
LN 1/2	0.241	0.510	0.62-1.606
Grade 3/1,2	0.021	4.981	1.607-12.637
Her2/neu+/-	0.601	1.241	0.871-2.987
Taxane/anthracycline-based chemotherapy	0.315	0.620	0.69-1.818

LN: Lymph node, HR: Hazard ratio, CI: Confidence interval

statistics and were compared using the chi-square. Kaplan-Meier method16 was used to estimate the local recurrence free survival LRFS and Disease-free survival (DFS). LRFS was measured from the date of diagnosis to the date of first Local recurrence in the ipsilateral breast while, (DFS) was measured from the date of diagnosis until date of first recurrence, loco-regional or systemic. The effects of clinical variables on local recurrence were assessed by univariate analysis. We used the log-rank test to compare the curves for univariate analysis. Follow-up duration was calculated from the date of diagnosis until the date of the event. A *P*-value <0.05 was considered significant and all *P*-values were two-sided. The statistical software used in this study was SPSS16 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

Between January 2005 and December 2012, 164 patients received breast conservation surgery followed by adjuvant therapy. The median age was 45 years (26-71) for group-1 and 44 years (25-65) for group-2. The patients and tumor characteristics are shown in Table 1.

Both groups had an approximately similar distribution regarding the percentage of hormone receptor status, different types of nuclear grade, and Her2/neu status. The only significant difference between the study groups was the number of patients who received Taxane -based chemotherapy, which was more in group-2 (stage III) patients (*P*=0.001).

Ipsilateral breast tumor recurrence rate (IBTR)

After a median follow-up of 40.4 months, 18 (15.5%) patients in group-1 and 8 (16.6%) in group-2 developed IBTR (*P*=0.77). The mean time to tumor recurrence was 19 months in group-1 and 17 months in group-2 (*P*=0.5).

Factors associated with ipsilateral breast tumor recurrence (IBRT)

We found significantly increased IBTR in patients with hormone negative tumors in group 1 (*P*=0.015) and group 2 (*P*=0.045). Young age (<40 years) at diagnosis was also associated with IBTR in group-1 (*P*=0.041) and 2 (*P*=0.01).

We also compared local recurrence according to tumor size, lymph node stage and nuclear grade in all patients and found no statistically significant difference between tumor size and local recurrence (*P*=0.240; Table 2 and Figure 1).

On the other hand, IBTR was significantly increased in patients with N1 nodal status compared to those who were N0 (*P*=0.011). We did not observe any statistically significant difference between patients with N1 and N2 nodes (*P*=0.241) as shown in Figure 2a and Figure 2b.

As mentioned above we found significant association between IBTR and Grade III (*P*= 0.012) also with negative hormonal expression (*P*=0.002) (Figure 3) and with young age (<40years) *P*=0.017. There was no statistically significant association between Her2/neu status, type of adjuvant chemotherapy regimen and IBTR.

Cosmetic appearance

Cosmetic appearance after removal of a tumor

5 cm tumor was reported as excellent by 35 (72.9%) and good by 7 (14.5%). Although 6 (12.5%) patients reported the cosmetic appearance as bad, these patients stated they were happy that the affected breast was not removed.

Discussion

The use of preoperative chemotherapy is the accepted standard treatment approach for patients with inflammatory breast cancer; also it is increasingly being used in women with locally advanced disease and in patients with operable earlier-stage breast cancer.[17] However, a meta-analysis of nine trials has not shown any statistically or clinically significant difference between adjuvant and neoadjuvant arms.[18, 19] In contrast, neoadjuvant therapy was associated with a statistically significant increased risk of locoregional recurrence when followed by RT alone and no surgery in patients who had complete clinical response after neoadjuvant therapy.[18] These results have confirmed that surgery remains an essential part of early breast cancer management, even when systemic therapy appears to have eradicated all grossly evident disease.[20, 21]

We have conducted this study to assess the outcome of stage IIIA patients who preferred surgery without preoperative chemotherapy and compared it with other stages regarding local ipsilateral recurrence.

Our results did not show any statistical significant between IBTR and tumor size (P=0.240). This finding was comparable with results of a study by Fitzal et al.[13] where the authors stated that BCS was possible in patients with T3 and T4 breast cancer as long as they received post-operative radiation and systemic therapy. Although the NCCN guidelines[10] did not include stage IIIA (T3, N1, M0) subtype as an obligatory indication for neadjuvant therapy, they recommended that the other stage IIIA subtypes receive neoadjuvant treatment. This recommendation emphasized lymph node status rather than tumor size. However this is controversial because as long as the level I and II of axillary LN will be removed in the surgery, thus the local recurrence will not be affected by the presence or absence of the neadjuvant therapy .

We found a significant increase in IBTR in patients with N1 status compared with N0 patients (P=0.011). These results have been confirmed by several studies.[22,23] Despite the advanced node stage is a risk factor for distance metastases, we did not observe any significant difference between N1 and N2 regarding local recurrence. This result has been previously reported in a study conducted by Beadle et al.[24] These researchers concluded that patients with N1 and N2 nodes have equal risk in terms of local recurrence.

We found that negative hormone receptors were associated with significant increase in local recurrence (P=0.002). This finding has been previously reported in several studies.[25-27] In terms of Her2/neu status, we did not observe any significant correlation between its expression and local recurrence. Other studies have conflicting results; some authors have suggested that IBTR significantly increased with positive Her2/neu expression[25] whereas others suggested it was more in triple negative breast cancer (TNBC), particularly the basal type.[26] Recently it has been explained by the relative radio resistance of the TNBC subtype as a consequence of ER-negative receptor status. It was suggested that ER-negative cells which are present in TNBC-and basal-like breast cancer exhibit radioresistance as DNA repair is allowed to progress during the slower cell cycle.[27] Therefore, it is mainly dependent on ER status rather than Her2/neu status.

Our results showed that patients <40 years of age had more local recurrence than older patients (P=0.0171). This has been reported in many studies. Some studies consider age as an independent risk factor for local recurrence.[28, 29]

In terms of cosmetic appearance, we found that patients who had an average body mass index of 29 kg/m^2 (range: 27-33) expressed satisfaction with the cosmetic appearance, whereas the other 6 patients who did not achieve satisfactory cosmetic appearance had an average body mass index of 23 kg/m^2 (range: 21-26). We explained that the elevated body mass index was associated

with large breast volume which made the cosmetic appearance better compared to patients with low body mass index.

Conclusion

Our study has shown that BCT with level II axillary dissection, post-operative RT and systemic chemotherapy can be a feasible option for stage IIIA breast cancer even without primary systemic therapy, providing post-operative RT and chemotherapy are administered. However, age, hormonal status, Her2/neu expression and lymph node status should be considered as risk factors for local recurrence. Cosmetic appearance can be maintained by considering breast volume and body mass index. An additional study that enrolls more patients is recommended to confirm our results.

Conflict of interest

No conflict of interest is declared.

Authors' contributions

Abeer Ibrahim performed the literature search, drafted and wrote the paper. Anwar Amin drafted the research protocol, provided guidance for the drafting of the paper and assisted with data collection. Rehab Hassan performed data collection and data entry. All authors read and approved the final paper.

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