Factors contributing to local recurrence after conservative breast surgery for early-stage breast cancer

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Background
Breast-conserving surgery is the standard procedure for early breast cancer. Local recurrence after conservation is the main problem, and many factors can predict this local recurrence.
Aim
To highlight factors that may contribute to local recurrence after conservative breast surgery for early breast cancer in our Egyptian patients.
Patients and methods
A prospective cohort study was conducted that included 137 patients from breast clinic, Ain Shams University Hospitals. All patients were candidates for conservative breast surgery for primary early-stage breast cancer. They were followed up from January 2016 to December 2017 based on a fixed schedule.
Results
Incidence of local recurrence was 2.9%. Mean time to local recurrence was 14 months (range: 12–16 months). Tumor grade and estrogen receptor and progesterone receptor status were the most important prognostic factors affecting local relapse. On the contrary, age, family history, tumor size, safety margin, tumor type, lymph node (LN) status, HER-2 status, Ki-67, and intraductal component did not have a significant effect on local recurrence.
Conclusion
Patients with high-grade tumors, estrogen receptor and progesterone receptor negativity should be treated aggressively. As all cases of local recurrence occurred in the first 16 months in our study, we strongly recommend that the scheduling of surveillance visits should be more frequent during the first 2 years (at least every 3 months).

Keywords:
conservative breast surgery, early breast surgery, local recurrence

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Introduction

Breast cancer is one of the most common malignancies in women, accounting for 22.9% of all female cancers worldwide [1] and 37.7% in Egypt [2]. It is considered a principal cause of death from cancer among women globally. In Egypt, it carries an unfavorable prognosis, with 29% mortality and 3.7 : 1 incidence to mortality ratio [2].

Breast-conserving surgery followed by a course of postoperative radiotherapy is considered to be the current standard of care for patient with early operable breast cancer [3], because the use of breast conserving procedure is associated with a high quality of life for most of patients, and its popularity comes from the result of the increasing awareness of and participation in early detection programs. This procedure includes quadrantectomy or wide local excision combined with ipsilateral axillary nodal dissection followed by radiotherapy.

Modified radical mastectomy continues to be appropriate for some patients, but breast conservation therapy is now regarded as the optimal treatment for most of the patients [4]. Several randomized trials with very long follow-ups have established that breast-conserving therapy and mastectomy share equivalent outcomes in terms of overall survivals.

The greatest concern in breast-conserving surgery remains the local recurrence, which can provoke serious anxiety to the patient [5]. Large variations in the breast recurrence rate at 5 years following breast conserving treatment for invasive breast carcinoma have been reported (2–22%) from different centers. The majority of these recurrences (~80%) occur adjacent to the site of initial excision [6].

An important treatment-related risk factor for local recurrence is the adequacy of surgical excision. This is

demonstrated by the fact that most recurrence after breast conservative surgery occurs at the same side of and are clonally related to their primary lesions [7].

In our study, we will report our experience with 137 patients with early breast cancer who are candidates for conservative breast surgery to detect factors contributing to local recurrence.

Patients and methods

This is a prospective cohort study that included 137 patients, who were recruited from breast clinic in El-Demerdash and Ain Shams University Specialized Hospital, Cairo, Egypt. They were followed up from January 2016 to December 2017. All patients were candidates for conservative breast surgery for primary early-stage breast cancer (clinically T1–T2, N0–N1, M0). Written informed consent was taken from all the patients who accepted to participate in the study. Approval by Research Ethics Committee, Ain Shams Faculty of Medicine, was obtained.

Inclusion criteria

The inclusion criteria were as follows:

(1) Early breast cancer: clinicallyT1–T2, N0–N1, M0.
(2) Patient is candidate for breast conservation.

Exclusion criteria

The exclusion criteria were as follows:

(1) Contraindication for breast conservation, for example, large tumor more than 5 cm, huge breast, multicentricity, multifocality, and contraindication to radiotherapy, for example, pregnancy and collagen disease.
(2) Patient's refusal.
(3) Tumor stage more than T2, N1, M0.
(4) Neoadjuvant treatment.
(5) Synchronous or metachronous malignancy in other organs.

Methods

All patients included in the study were subjected to the following:

Preoperative workup

(1) History taking: Age of the patient; menstrual history including age of menarche and menopause; complaint of the patient, for example, breast masses, pain, and nipple discharge; history of contraceptive agents; family history of breast cancer; and metastatic symptoms like chest wall pain, cough, or backache.
(2) Examination: Full general examination was done focusing on signs of metastases such as bony tenderness, pleural effusion, pathological fracture of limbs, enlarged liver, and skull metastases.
(3) Both breasts and axilla were examined thoroughly with full comment including site, size, mobility of tumor, and relation to surroundings, as seen in Fig. 1.
(4) Investigations:
    (1) Laboratory: routine preoperative investigations, for example, complete blood count, coagulation profile, and blood chemistry.Radiological: bilateral breast sonomammography, as seen in Fig. 2, pelvi-abdominal ultrasonography, chest radiography, and MRI of the breast when needed.Biopsy: either tru-cut biopsy, frozen section and proceed, or excisional biopsy.

Figure 1

Two of our patients show a mass on examination. The skin overlying is marked.

Before surgery, all cases were discussed during the weekly multidisciplinary meeting attended by surgeons, clinical oncologists, radiologists, and pathologists. The decision for the surgical intervention and adjuvant systemic treatment was made according to the preformed protocol established by the multidisciplinary team.

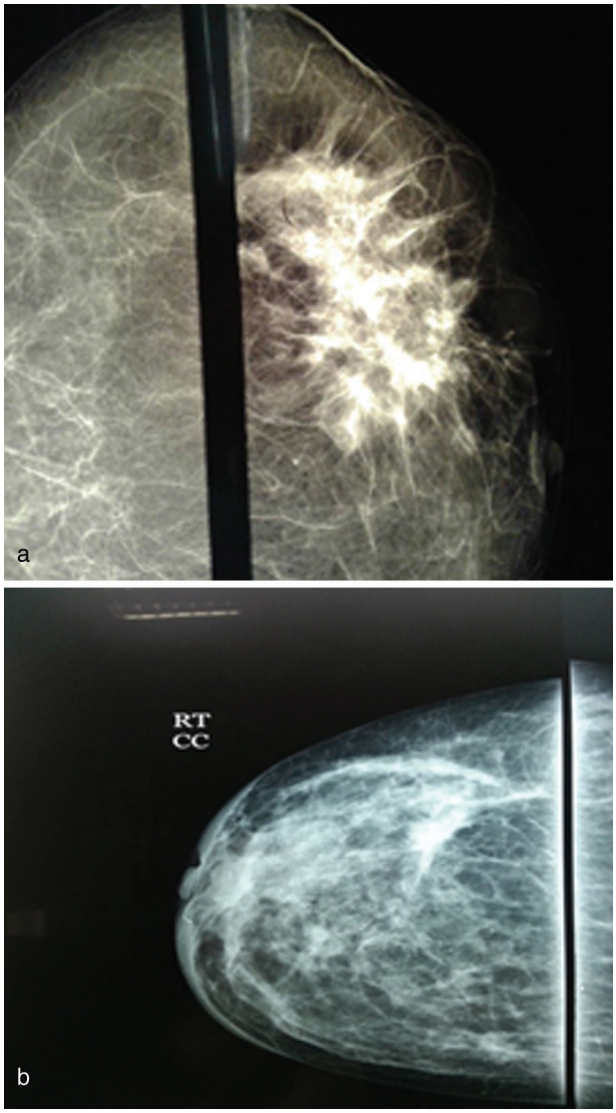
Operative procedure

All patients underwent conservative breast surgery in the form of wide local excision or quadrantectomy and axillary lymph node (LN) dissection levels I and II under general anaesthesia, in supine position with arm abducted to 90°. First, prompt identification of the patient and marking of the side of operation with review of the patient's medical file were done. Properly designed incision including the tumor and the overlying skin with safety margin all around was made. Excision of the mass with at least gross safety margin of 1 cm was done. Marking of the specimen margins was done with nonabsorbable suture. Overall, 3–4 clips, which are used in laparoscopic cholecystectomy, are inserted in the tumor bed.

Separate axillary incision below the axillary crease if the axilla is not accessible within the primary incision, axillary lymph node dissection below and behind pectoralis minor (level I and II only), excision of the axillary specimen in a downward direction below the axillary vein preserving the long thoracic nerve and the thoracodorsal bundle, as seen in Fig. 3, lavage of the operative beds with normal saline with meticulous hemostasis. Suction drain application in both tumor and axillary beds is done. Closure of the subcutaneous and cutaneous layers was done, as in Fig. 4.

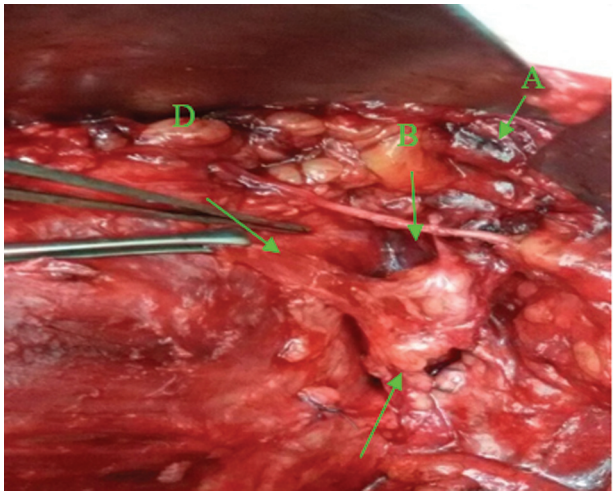
Preservation of the specimens in formalin along with labelling and sending for histopathological examination accompanied with a full report, as in

Figure 2



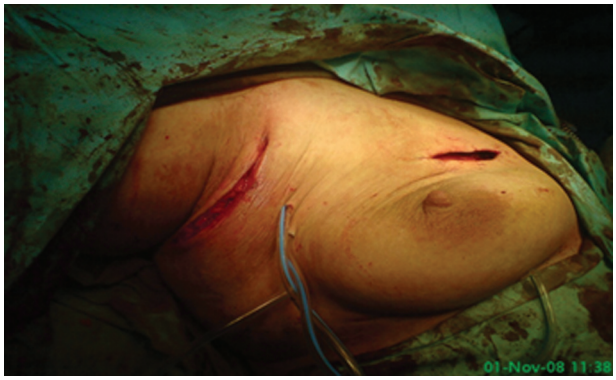
Two mammograms show suspicious mass with speculated margin.

Figure 3



After axillary dissection. (a) Axillary vein. (b) Intercostal brachial nerve. (c) Thoracodorsal bundle. (d) Long thoracic nerve.

Figure 4



Incisions for lumpectomy and axillary LN dissection.

Fig. 5, was done. In cases of involved margins, wider excision was done using frozen section to guarantee adequate margin control.

Postoperative workup

We obtained full histopathological report including mass size, histological type and grade, safety margins, extent of the intraductal component, LN status, receptor status [estrogen-receptor (ER), progesterone receptor (PR), and HER-2 neu], and Ki-67.

All patients received adjuvant radiotherapy to the whole breast with boost doses to tumor bed. Adjuvant chemotherapy was tailored according to the individual condition of each patient. It was indicated in patients having axillary lymph node metastasis or a tumor larger than 1 cm. Adjuvant hormonal therapy (tamoxifen or aromatase Inhibitor) was given to ER/PR-positive patients. Patients with HER-2 overexpression received trustuzumab.

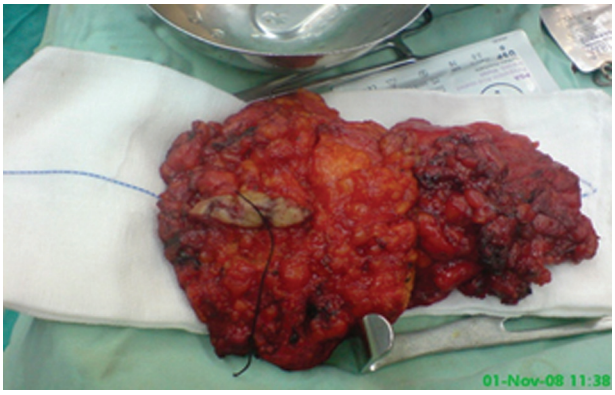
During the follow-up, the patients were seen in the outpatient clinic as follows:

(1) Every three months by history taking and full clinical examination with particular attention to the tumor bed.
(2) Every 6 months by sonomammography.
(3) Pelvi-abdominal ultrasonography and chest radiography every 6 months.
(4) Tissue biopsy and MRI were required to confirm local recurrence in suspected cases.
(5) Bone scan when needed (bone aches or high alkaline phosphatase).

Data collection

Data were collected prospectively from patient records and medical files and were analyzed.

Figure 5



Specimens are marked with silk before preservation.

Outcome measures

Local recurrence was defined as recurrence in the original tumor bed with the same histopathologic features of the primary tumor.

The end point was directed to the detection of factors that may contribute to local recurrence after conservative breast surgery, which are as follows:

(1) Age of the patient.
(2) Family history of breast cancer.
(3) Mass size.
(4) Surgical margin.
(5) Histological type.
(6) Histological grade.
(7) LN status.
(8) Receptor status (ER, PR, and HER-2 neu).
(9) Ki-67.
(10) In-situ component.

Data management and analysis

The collected data were revised, coded, tabulated, and introduced to a PC using statistical package for the social sciences (SPSS 15.0.1 for Windows; SPSS Inc., Chicago, Illinois, USA). Data were presented, and suitable analysis was done according to the type of data obtained for each parameter.

(1) Descriptive statistics:
    (1) Mean±SD and range for parametric numerical data.Frequency and percentage of non-numerical data.
(2) Analytical statistics:
    (1) Student t-test was used to assess the statistical significance of the difference between two study group means.Fisher's exact test was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells.

The level of significance (*P* value) was as follows:

(1) *P* value more than 0.05: nonsignificant.
(2) *P* value less than 0.05: significant.
(3) *P* value less than 0.01: highly significant.

Results

Results of perioperative workup

Results of clinical examination

Among the 137 cases enrolled in our study, 133 (97%) patients presented with accidentally discovered breast lump, whereas only four (3%) patients had impalpable lesions that were discovered by imaging studies done for other symptoms, for example, mastalgia. A total of

23 (16.8%) patients had clinically palpable mobile ipsilateral axillary lymph nodes.

Results of investigations

All patients were subjected to bilateral sonomammography which revealed suspicious masses in most of patients and clustered microcalcification in 13 (9.5%) patients. MRI of the breast was needed only in the follow-up of eight (5.8%) cases.

Regarding histopathological reports, 129 (94.2%) patients had in situ ductal carcinoma (IDC), 122 (88.9%) with grade II, 126 (92%) with mass more than 2 cm, 115 (83.9%) with safety margin between 0.1 and 1 cm, and 72 (52.6%) cases with pN0.

Results of treatment modalities

All patients underwent conservative breast surgery in the form of either wide local excision or quadrantectomy and axillary clearance, levels I and II. Only three (2.2%) cases had infiltrated margins in pathology reports (<1 mm) and, hence, underwent wider excision achieving adequate margins. There was no recorded mortality. Postoperative morbidity was seroma in 32 (23.4%) cases, wound infection in 13 (9.5%) cases, and arm edema in seven (5.1%) cases.

All cases received adjuvant radiotherapy to the whole breast using the conventional regimen (overall dose 50 Gy). Boost doses to tumor bed was given in all cases, with doses ranging from 5 to 10 Gy.

Regarding chemotherapy, 113 (82.5%) patients received anthracycline-based regimen with or without taxane-based regimen, seven (5.1%) cases received CMF regimen, whereas 17 (12.4%) cases did not receive chemotherapy according to the protocol of the multidisciplinary team. Patients with positive hormonal receptors were prescribed tamoxifen (20 mg/day) in 90 (65.7%) cases and aromatase inhibitor in 23 (16.8%) cases for 5 years. Only 11 (8%) patients with HER-2 over expression received trustuzumab.

Descriptive data analysis

The mean age of study cases was 51.4±11.2 (range: 27–81) years, with ~79% of cases showing negative family history of breast cancer. Mean follow-up interval was 21 months (range: 18–24 months) (Table 1).

Table 2 shows that 126 (92%) women had a tumor more than 2 cm in diameter, 115 (83.9%) had a safety margin between 0.1 and 1 cm, 109 (79.6%) had positive-ER disease, and 111 (81%) had positive-PR disease. A total of 129 (94.2%) women had IDC, 122 (88.9%) had histological grade II, and 72 (52.6%) cases had no infiltrated LN.

Table 1 Description of personal data

	Mean±SD	Minimum	Maximum
Age	51.45±11.24	27.00	81.00
Family history [*n* (%)]			
Negative	108 (78.8)		
Positive	29 (21.2)		

Table 2 Study population characteristics

	Mean±SD	Minimum	Maximum
Size (cm)	2.67±1.01	0.50	5.00
Margin (cm)	0.91±.65	0.10	4.00
Ki-67	14.83±10.88	1.00	70.00
In-situ component	11.81±16.90	0.00	90.00
Size [*n* (%)] (cm)			
<2	11 (8.0)	–	–
≥2	126 (92.0)	–	–
Margin [*n* (%)] (cm)			
0.1–1	115 (83.9)	–	–
1–2	18 (13.1)	–	–
>2	4 (2.9)	–	–
Ki-67 [*n* (%)]			
≤14	67 (48.9)	–	–
>14	70 (51.1)	–	–
In-situ component [*n* (%)]			
≤25	122 (89.1)	–	–
>25	15 (10.9)	–	–
Estrogen receptor [*n* (%)]			
Negative	28 (20.4)	–	–
Positive	109 (79.6)	–	–
Progesterone receptor [*n* (%)]			
Negative	26 (19.0)	–	–
Positive	111 (81.0)	–	–
HER [*n* (%)]			
Negative	126 (92.0)	–	–
Positive	11 (8.0)	–	–
Type [*n* (%)]			
IDC	129 (94.2)	–	–
ILC	6 (4.4)	–	–
Others	2 (1.5)	–	–
Grade [*n* (%)]			
Grade 1	2 (1.5)	–	–
Grade 2	122 (88.9)	–	–
Grade 3	13 (9.6)	–	–
LN status [*n* (%)]			
pN0	72 (52.6)	–	–
pN1	26 (19.0)	–	–
pN2	22 (16.1)	–	–
pN3	17 (12.4)	–	–
Recurrence [*n* (%)]			
Negative	133 (97.1)	–	–
Positive	4 (2.9)	–	–

IDC, in situ ductal carcinoma; ILC, in situ lobular carcinoma; LN, lymph node.

During the follow-up period, we observed four cases of local recurrence with cumulative incidence rate of 2.9%, as shown in Fig. 6. Mean time to local recurrence was 14 months (range: 12–16 months). Mortality rate was 5.1% (seven cases): three of them owing to systemic spread whereas the others owing to non-cancer-related causes.

Correlation of local recurrence to patient variables

There was no significant difference regarding mean age between recurrent and nonrecurrent patients, as illustrated in Table 3.

Regarding family history of breast cancer, no significant difference was found as none of cases with positive family history had recurrence compared with 3.7% of cases with negative family history, as seen in Table 4.

Size of the tumor had no statistically different effect on local recurrence, although the four recurrent cases had tumour size more than 2 cm. Only 3.2% of patients with masses larger than 2 cm had local recurrence compared with 96.8% who did not have, as in Table 5.

Regarding the LN status, there was no statistically significant difference as only 2.6% of cases with pN2/N3 had local recurrence compared with 3.1% of those with pN0/N1 (Table 6).

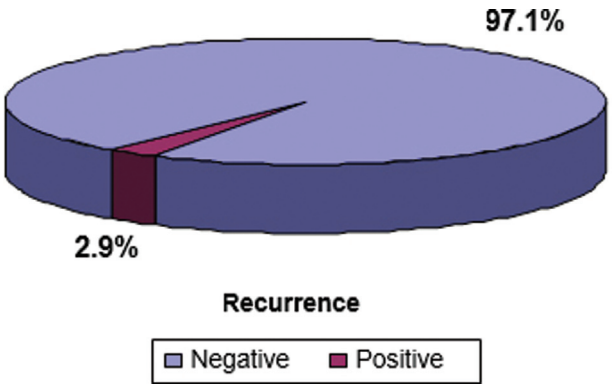
In-situ component status showed no significant difference. As seen in Table 7. However, women with in-situ component more than 25% have 2.8 times higher risk for local recurrence than those with in-situ component less than 25%.

Overall, 50% of recurrent cases had a safety margin between 0.1 and 1 cm, whereas the other half had a safety margin ranging between 1 and 2 cm. However, this difference did not reach statistical significance (Table 8).

Approximately 3.1% of patients with IDC had local recurrence compared with none of those with in situ lobular carcinoma (ILC) and other types, with no statistically significant difference (Table 9).

There was a significant difference regarding tumor grade as 30.8% of grade III cases had recurrence

Figure 6



Incidence of local recurrence.

Table 3 Relation between mean age and local recurrence

	Recurrence (mean±SD)		P^a	Significant
	Yes	No		
Age	57.75±8.10	51.26±11.29	0.257	NS

[a]Student's *t*-test.

Table 4 Relation between family history and local recurrence

	Family history [n (%)]		P^a	Significant
	Positive	Negative		
Recurrence				
Yes	0 (0.0)	4 (3.7)	0.578	NS
No	29 (100.0)	104 (96.3)		

[a]Fisher exact test.

Table 5 Relation between tumour size and local recurrence

	Size [*n* (%)] (cm)		*P*	Significant
	<2	≥2		
Recurrence				
Yes	0 (0.0)	4 (3.2)	1.0[a]	NS
No	11 (100.0)	122 (96.8)		

[a]Fisher exact test.

Table 6 Relation between LN status and local recurrence

	LN status [*n* (%)]		P^a	Significant	Odds ratio (confidence interval)
	pN0/N1	pN2/N3			
Recurrence					
Yes	3 (3.1)	1 (2.6)	1.0	NS	1.2 (0.1–11.9)
No	95 (96.9)	38 (97.4)			

LN, lymph node. [a]Fisher exact test.

Table 7 Relation between tumour in-situ component and local recurrence

	In-situ component [*n* (%)]		*P*	Significant	Odds ratio (confidence interval)
	≤25	>25			
Recurrence					
Yes	3 (2.5)	1 (6.7)	0.36[a]	NS	0.35 (0.03–3.6)
No	119 (97.5)	14 (93.3)			

[a]Fisher exact test.

Table 8 Relation between safety margin and local recurrence

	Safety margin [*n* (%)] (cm)			*P*[a]	Significant
	0.1–1	1–2	>2		
Recurrence					
Yes	2 (1.7)	2 (11.1)	0 (0.0)	0.1	NS
No	113 (98.3)	16 (88.9)	4 (100.0)		

[a]Fisher exact test.

Table 9 Relation between histologic type and local recurrence

	Grade [*n* (%)]			*P*[a]	Significant
	IDC	ILC	Others		
Recurrence					
Yes	4 (3.1)	0 (0.0)	0 (0.0)	1.0	NS
No	125 (96.9)	6 (100.0)	2 (100.0)		

IDC, in situ ductal carcinoma; ILC, in situ lobular carcinoma.
[a]Fisher exact test.

Table 10 Relation between histologic grade and local recurrence

	Type [*n* (%)]			*P*	Significant
	Grade 1	Grade 2	Grade 3		
Recurrence					
Yes	0 (0.0)	0 (0.0)	4 (30.8)	0.001[a]	HS
No	2 (100.0)	120 (100.0)	9 (69.2)		

[a]Fisher exact test.

compared with none of those with grade I–II (P=0.001) as shown in Table 10 and Fig. 7.

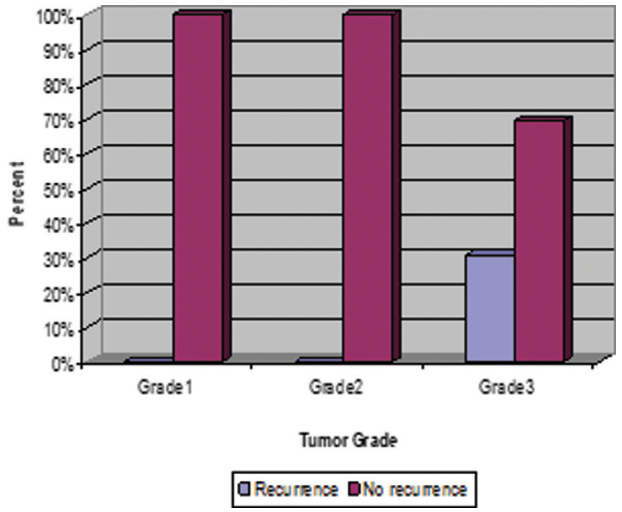
ER status affected local recurrence significantly, as 10.7% of patients with negative ER had local recurrence compared with only 0.9% of those with positive ER. Negative ER cases had 12.9 times higher risk for local recurrence than positive ER cases (P=0.027) (Table 11 and Fig. 8).

In parallel, there was a significant difference regarding PR status, as 11.5% of cases with negative PR had recurrence compared with only 0.9% of those with positive PR. Negative PR patients had 14.3 times higher risk for local recurrence than positive PR cases (P=0.022) (Table 12 and Fig. 9).

Regarding the HER status, there was no significant difference as local recurrence occurred in 2.4% of patients with negative HER compared with 9.1% of those with positive HER, as seen in Table 13.

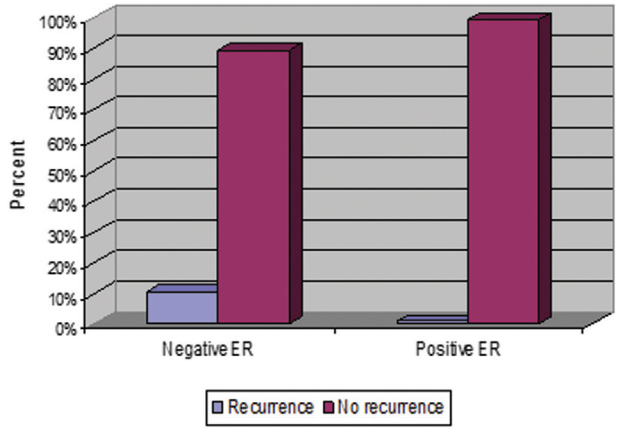
Although 5.7% of patients with Ki-67 more than 14% had recurrence compared with none of those with Ki-67 less than 14%, this difference did not appear to be statistically significant (Table 14).

Figure 7



Local recurrence among histological grades.

Figure 8



Local recurrence among estrogen receptor-positive and estrogen receptor-negative cases.

Table 11 Relation between estrogen receptor status and local recurrence

	Estrogen receptor [*n* (%)]		*P*	Significant	Odds ratio (confidence interval)
	Negative	Positive			
Recurrence					
Yes	3 (10.7)	1 (0.9)	0.027[a]	S	12.9 (1.2–129.8)
No	25 (89.3)	108 (99.1)			

[a]Fisher exact test.

Although a multivariate analysis would be desirable, we did not perform it because of the limited numbers of local recurrence cases.

Discussion

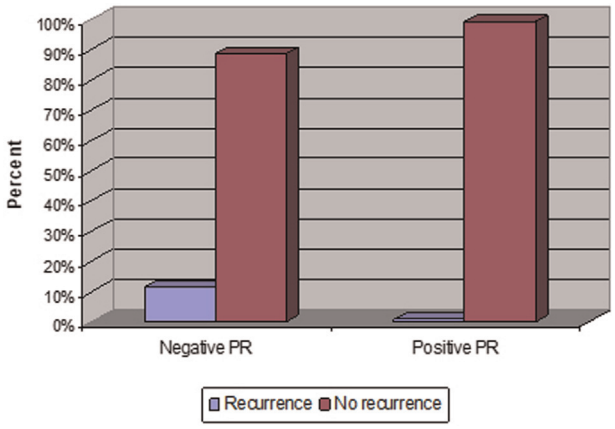
The revolution of the surgical treatment of breast cancer during the past decades has led to the progressive

Table 12 Relation between progesterone receptor status and local recurrence

	Progesterone receptor [*n* (%)]		*P*	Significant	Odds ratio (confidence interval)
	Negative	Positive			
Recurrence					
Yes	3 (11.5)	1 (0.9)	0.022[a]	S	14.3 (1.4–144.1)
No	23 (88.5)	110 (99.1)			

[a]Fisher exact test.

Figure 9



Local recurrence among progesterone receptor-positive and progesterone receptor-negative cases.

Table 13 Relation between HER status and local recurrence

	HER [*n* (%)]		*P*	Significant	Odds ratio (confidence interval)
	Negative	Positive			
Recurrence					
Yes	3 (2.4)	1 (9.1)	0.2[a]	NS	0.24 (0.02–2.5)
No	123 (97.6)	10 (90.9)			

[a]Fisher exact test.

Table 14 Relation between tumor Ki-67 and local recurrence

	Ki-67 [*n* (%)]		*P*	Significant
	≤14	>14		
Recurrence				
Yes	0 (0.0)	4 (5.7)	0.12[a]	NS
No	67 (100.0)	66 (94.3)		

[a]Fisher exact test.

reduction of the extent of surgery [5]. Consequently, the quality of life has improved and women are now more motivated to follow screening programs for early diagnosis of the disease and hence avoiding mastectomy. The greatest concern in breast-conserving surgery remains the local recurrence, which can provoke serious anxiety to the patient and, when treated by mastectomy, negate the objective of conservation [8].

In the Danish and US National Cancer Institute and Gustave Roussy Institute trials, recurrence-free, disease-free, and overall survivals were not significantly different between the BCS and MRM arms [9]. In contrast to this trial, in the Milan trial, local recurrence in 20-year follow-up period was 8.5% in the BCS arm and 2.8% in the MRM arm [10].

The incidence rate of local recurrence in our research was 2.9%. It was close to the incidence rate in the study by Erhan and Haluk [11], which was 3.7%. It should be noted that they investigated nearly the same sample size as we had. Our incidence rate appeared to be lower, and subsequently, better than that of Aristei *et al.* [12] and Houssami *et al.* [13], which was 4.7 and 7%, respectively. Nevertheless, our duration for follow-up was at a mean of 21 months (range: 18–24 months) which was much shorter than that of others. For example, in the study by Aristei *et al.* [12], the median follow-up for the entire cohort was 87 months (range: 21–120 months).

Time to recurrence was a significant prognostic factor of systemic progression [14]. In our study, local relapse occurred at a mean of 14 months (range: 1–1.3 years). In another study, local relapse occurred at a median of 4.2 years (range: 1.0–9.3 years) after CBS [12]. This difference in the onset of local recurrence may be related to the tumor aggressiveness of our patients.

In our study, the mean age of study cases was 51.4±11.2 (range: 27–81) and age was not found to be a predictor for local recurrence (LR). There are some conflicting reports about the incidence of local recurrence between age groups. Our finding was supported by Erhan and Haluk [11] who studied 135 cases, with mean age of the patients being 46.6 years (range: 24–75 years), and noticed that young age was not found to be predictive for LR. In addition, it was reported that there was no statistical significance in the local recurrence rate (LRRs) between the two age groups, although those younger than 50 years presented with a higher LRR than those older than 50 years [15].

In contradiction, Botteri *et al.* [5] reported that young age increased the risk of local recurrence. Kim *et al.* [16] found that age affected the local control, and patients with multiple unfavorable risk factors such as positive axillary lymph nodes (P=0.01) and young age (P=0.02) showed poorer local control than in patients without any risk factors. In their multivariate analyses, it was stated that age was an independent predictor of local relapse. In their patients, the local recurrence risk fell as age increased, so older age was a protective factor for

local recurrence [12]. This contrast may be possibly correlated to differential treatment strategies or biological features of tumors depending on age, as older patients may have tumors with more favorable biology. Moreover, our follow-up time was too short to enable us to detect the correlation between young age and local recurrence.

There was a significant correlation between tumor grade and LR in our patient series, but tumor type did not affect LR. In a large trial by EORTC including 5569 patients, young age and high-grade invasive ductal cancer were the most important risk factors for local relapse, whereas margin status had no significant influence. A boost dose of 16 Gy significantly reduced the negative effects of both young age and high-grade invasive cancer [17]. Higher tumor grade and larger tumor size have been linked to increased local recurrence risk, but not as consistently as age [18]. On the contrary, Lee *et al.* [15] found no influence of tumor type and histological grade on the risk of local recurrence.

Regarding tumor size, we did not find a significant correlation with LR. Moreover, Kim *et al.* [16] found that the T stage did not affect local recurrence. On the contrary, Lee *et al.* [15] found that the mean tumor size was 2.0 cm and overall T stages contributed significantly to the LRR of breast cancer ($P<0.001$). In addition, size was associated with local recurrence in Botteri's study [5].

In our cases, resection margin status, one of the important prognostic factors affecting local control, did not influence local recurrence rates. Moreover, it did not affect local-relapse-free survival in the study of Kim *et al.* [16]. In parallel, it was reported that a close resection margin is not likely to affect local relapse. They reported that patients with close margins and those with negative margins both had a rate of local recurrence of 7% at 8 years [19].

In the study conducted by Lee *et al.* [15], positive margin status, multiple margin positivity, and T/N stages showed statistical significance in univariate analysis. However, only multiple margin positivity was identified as an independent risk factor for local recurrence in multivariate analysis. Consequently, when the multiple margin positivity is diagnosed on intraoperative frozen biopsy, surgeons should consider a much wider excision of the breast and a more aggressive management. The surgical margin status has been accepted to be the most important risk factor, because it is the only risk factor which is controllable by surgeons. A plausible interpretation to this study is that margin positivity is always associated with residual cancer cells in the tumor bed.

In multivariate analyses, resection margin status was an independent predictor of local relapse in the study of Aristei *et al.* [12]. More recently, Houssami *et al.* [13] performed a meta-analysis of 21 trials including 14 571 women with early breast cancer treated with breast conservative treatment (BCT) (1026 of whom developed local recurrence). The pooled data demonstrated that a positive margin or a margin less than 1 mm was associated with increased risk of local recurrence, but the odds of local recurrence did not differ significantly with surgical margin widths greater than 1 mm. They concluded that a wider surgical margin is not always better, and a 1-mm surgical margin may be adequate in most circumstances. It is worthy to notify that, despite the large sample, these were mostly retrospective analyses. Moreover, this meta-analysis did not study many tumor and therapeutic factors that influence the risk of local recurrence after BCT, as we did.

In our work, we found that ER and PR positivity were associated with reduced incidence of local recurrence, whereas HER status did not show any influence on LRR. In consistency, ER status and HER-2/neu status were associated with local occurrence [5]. In fact, randomized phase III trials showed tamoxifen, given as adjuvant treatment, increased local control in ER-positive patients who had been treated with surgery and RT [20].

Information of hormone receptors was available in 444 (99.3%) cases, but no significant differences were found regarding recurrence. However, unlike previous reports, HER-2/neu positivity or triple negativity did not show a statistically significant association with LRR [15]. Positive receptor status was confirmed as a protective factor for nodal but not for local relapse. The protective effect of positive receptor status correlated closely with administration of hormonal therapy [12]. The lack of significance might be contributed to the small number of events in the latter study.

In their study with univariate analysis, Erhan and Haluk [11] reported that none of young age, lymph node involvement, and ER negativity were found to be predictive for LR. Based on their results, it would appear that with careful attention to both patient selection and surgical technique, BCS can be performed safely with a lower LR rate, particularly

in T1–T2 breast carcinoma cases, independent of any predictive factors. Although a multivariate analysis would be desirable, they did not perform that because of the limited numbers of end-point events.

Lymph node status was not correlated significantly with local recurrence in our research. The same result was concluded by Erhan and Haluk [11] who reported that lymph node involvement was not found to be predictive for LR. This similarity in results could be explained that the sample size is nearly identical in our and Erhan's studies (137 and 135 patients, respectively), although the median follow-up period in Erhan's study was longer at 54 months (range: 15–120 months) compared with our mean follow-up period which was only 21 months (range: 18–24 months).

However, Kim *et al.* [16] stated that the most important prognostic factor affecting local control was axillary lymph node metastasis. Therefore, patients with positive lymph nodes (P=0.01) should be treated aggressively. In multivariate analyses by Aristei *et al.* [12], the positive/excised node ratio was an independent predictor of local relapse.

Analysis of Ki-67 in our study did not reveal a correlation with LRR. Similarly, Ki-67 does not predict independently for locoregional outcomes after BCT when other prognostic clinicopathologic features such as age, race, hormone receptor status, and HER-2 status are taken into consideration [21]. On the contrary, it was reported that the Ki-67 index value was an independent prognostic factor in early breast cancer, particularly luminal type tumors [22]. A multivariate analysis by Reyal *et al.* [23] revealed that the Ki-67 index value remained the only significant prognostic factor in the subgroups of ER-positive and HER-2-negative tumors. Moreover, it was stated that Ki-67 was associated with local occurrence [5].

In a study on 4701 cases, analysis revealed that the Ki-67 index value in the primary tumor was an independent significant factor for breast cancer recurrence only in luminal type tumors. Therefore, the Ki-67 index value should be taken into consideration in the treatment and follow-up of patients with breast cancer [24]. In my opinion, these controversies could be explained by several limitations that affect the standardization of the Ki-67 index biomarker. One of the most important limitations is the variability of the Ki-67 cut-off point among studies and researchers. For example, our Ki-67 cut-off point was 14%, whereas in the study of Reiki *et al.* [24], it was 20%.

Regarding intraductal component, we did not find a correlation with local recurrence. Supporting our result, Hurd *et al.* [25] demonstrated that locoregional control was not adversely affected by the presence of an extensive intraductal component (>25%). However, this study can be criticised that it is old, retrospective, and of low sample size (133 patients only).

In contradiction, it was concluded that the presence of the intraductal component predicts a greater risk to develop LR. This risk increases significantly if extensive intraductal component is associated with G3 histological grade. Physicians must consider this fact in designing individually tailored adjuvant therapy for their patients. Special attention should also be paid to the follow-up of this group of patients [26]. Moreover, Kim and colleagues stated that the presence of extensive intraductal component affected the local-relapse-free survival rate (P=0.04) [12].

Conclusion and recommendations

Tumor grade and ER and PR status were the most important prognostic factors affecting local relapse of the breast cancer after conservative breast surgery. On the contrary, age, family history, tumor size, safety margin, tumor type, LN status, HER-2 status, Ki-67, and intraductal component did not have a significant impact on local recurrence, so we believe that, patients with high grade tumors, ER and PR negativity should be treated aggressively, and patients without any of these risk factors may require less aggressive treatment. As all cases of local recurrence occurred in the first 16 months in our study, we strongly recommend that the scheduling of surveillance visits should be more frequent during the first 2 years (at least every 3 months).

Limitations of our study

There are, of course, some limitations in our study. The follow-up period was only 2 years, and this was a single institution investigation with a small population. Four cases of local recurrence in our study are not a sufficient number for a reliable prediction. Hereafter, if a large population with long-term follow-up in multicentric investigation is performed, a much more concrete conclusion will be drawn.

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Conflicts of interest

There are no conflict of interest.

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