

# Recurrence after breast conserving surgery; can re-excision with intraoperative margin assessment normalize the risk of local recurrence?

*Ayman M S Soliman,<sup>a</sup> MD; Yasser Abdel Reheem,<sup>a</sup> MD;  
Osama M El-Shiekh,<sup>a</sup> MD; Ahmed M Awad Ellakany,<sup>a</sup> MD;  
Hala Rashad,<sup>b</sup> MD*

*a) Department of General Surgery, Ain Shams University, Cairo, Egypt.*

*b) Department of Pathology, Ain Shams University, Cairo, Egypt.*

## Abstract

*Background: Breast conserving therapy (BCT), including breast conserving surgery (BCS) and radiotherapy has become the preferred method of treatment for early stage breast cancer. Guidelines for breast conserving surgery (BCS) advise mastectomy if negative margins cannot be obtained after reasonable surgical attempts. The surgical margin status after breast-conserving surgery is considered the strongest predictor for local failure. This study aimed to evaluate the value of repeating breast conservative surgery versus total mastectomy in patients with intrabreast tumour recurrence (IBTR) and to identify factors predictive of the need for multiple re-excisions.*

*Methods: Between 2004 and 2008, 58 patients underwent BCS for stages 0–II breast cancer [invasive duct carcinoma, n = 42; ductal carcinoma in situ (DCIS), n =16] presented with intrabreast tumour recurrence (IBTR) which was the only sign of relapse. 49 patients were considered suitable for further surgery, 9 were inoperable. Group A; Twenty patients (40.8%) were suitable for repeating conservative surgery especially when intra-operative margin assessment included gross tissue inspection with frozen section done and negative margins were achieved. While in group B; the other 29 patients (59.2%), total mastectomies were done. The median follow-up after second surgery was 28 months (range 6-48).*

*Results: The two years local recurrence rates for groups A, B were 10% and 3.5% respectively, where presented in group A as IBTR and in group B as chest wall recurrence. Women <45 years underwent re-excision more frequently than other age groups. The overall 2 years survival rate was 86.2% after mastectomy and 85% after further local excision. Distant metastases developed in 13.8% and 5 % of mastectomy and re-excision groups respectively.*

*Conclusion: Re-excision was not disadvantageous in selected patients and selection should include small solitary recurrences in a breast large enough to permit satisfactory cosmetic results. Re-excision doesn't impact on local recurrence rates if negative margins are ultimately obtained. The patient should be consented about the risk of further intrabreast tumor recurrence (IBTR).*

*Key Words: Re-excision - Breast conserving surgery - Local recurrence - Breast cancer.*

## Introduction:

Most women with early-stage breast cancer can be successfully treated with breast conserving surgery (BCS). Although overall survival of women treated with BCS and radiation therapy (RT) is equivalent to mastectomy.<sup>1</sup> Histologically negative margins in women undergoing BCS are universally accepted as a way to reduce the risk of local recurrence (LR).<sup>2</sup> There is no standard definition of what constitutes a reasonable

number of surgical attempts to obtain a clear margin, and it is unknown whether the need for multiple re-excisions to obtain clear margins is associated with an increased risk of LR.<sup>3,4</sup> If the margins continue to be involved following primary re-excision, additional surgery is usually recommended; however, other than patient preference and habits, no clear guidelines exist as to whether the next procedure should be the resection of additional margins or a mastectomy. Mastectomy is the

current standard surgical treatment of intrabreast tumour recurrence (IBTR).<sup>5</sup> However the risk of local recurrence was not found to be eliminated with mastectomy and approximately 2-32% of patients treated with mastectomy develop a chest wall recurrence.<sup>2</sup> In the literature, the frequency of residual invasive or insitu carcinoma in re-excision specimens ranges from 32% to 63%.<sup>5,6</sup> In a previous study; some factors were identified which correlated with residual cancer in the primary re-excision specimen.<sup>7</sup> These included large tumor size, high tumor grade, young patient age, the presence and increased number of positive surgical margins, and single-mark versus 6-mark specimen suturing.<sup>7</sup>

Our hypothesis was that, as long as negative margins were ultimately achieved with intra-operative margin assessment, the number of re-excisions required to obtain the negative margin would not be associated with an increased risk of LR. This study aimed to evaluate the value of repeating breast conservative surgery versus total mastectomy in patients who had been treated previously by conservative operation (quadrantectomy or lumpectomy with axillary clearance and radiotherapy) and presented with intrabreast tumour recurrence (IBTR) and no other metastases, to examine the relationship between the need for multiple re-excisions and the risk of LR, and to identify factors predictive of the need for re-excision.

## Methods:

The study was conducted in El Demerdash and Ain Shams Specialized Hospitals from October 2004 to July 2008 on 58 patients with mean age  $55 \pm 13$  and presented by intrabreast tumour recurrence (IBTR) after BCS and postoperative radiotherapy (RT) for stages 0–II breast cancer (invasive duct carcinoma, n = 42; ductal carcinoma in situ (DCIS), n = 16); 22 patients were operated upon by quadrantectomy, axillary clearance and radiotherapy and 36 patients were subjected to lumpectomy, axillary clearance and radiotherapy **Figure(1)**. Chemotherapy at that time was not given (stage IIA; T2, N0 and stage IIB; T3, N0). On follow up; 28 patients presented by recurrent palpable lump in breast **Figure(2)**, in 24 patients recurrence was detected by sonomammographic follow up **Figure(3,4A)**, while the other 6 patients presented by increase in the marker level and the recurrent lesions which were detected by breast magnetic resonance imaging (MRI) **Figure(4B)**. The intrabreast tumor recurrence in the 58 patients was confirmed either by fine needle aspiration and cytological examination (FNAC) or open biopsy in patients diagnosed by MRI **Figure(5)**. Thorough clinical examination and investigations excluded other metastases. Also, nine patients from those 58 patients were considered inoperable as the breast was diffusely affected.

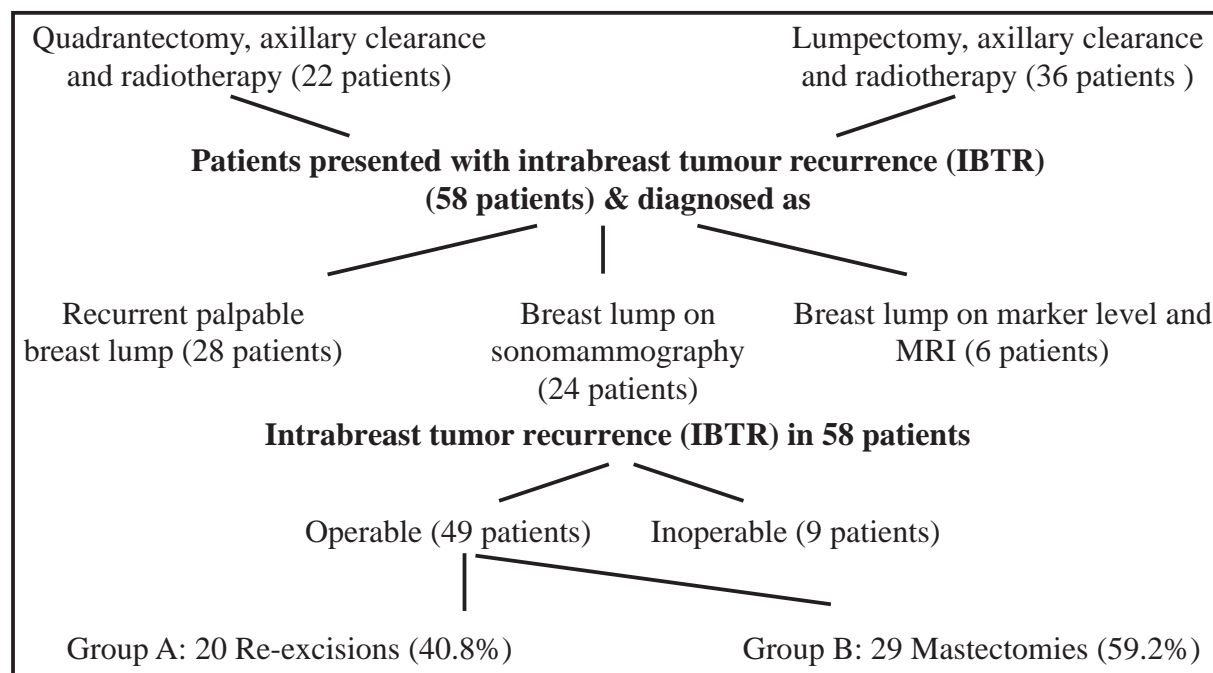


Figure (1): Treatment course of 58 breast cancer patients required re-excision or mastectomy following initial breast conservation.

The remaining 49 women were suitable for further surgery. Twenty patients (group A) were re-operated upon by re-excisions with breast conservation and inclusion criteria include; those patients had solitary tumor recurrence at the site of primary excision or <2cm from the scar with size less than 2 centimeters in its largest diameter and the size of breast permitted satisfactory cosmetic results. Multicentricity was excluded by mammography while MRI done in 6 patients only. Intra-operative margin assessment included gross tissue inspection, with frozen section done to ensure negative margins. While in the other 29 patients (group B) the previous selective data were not fulfilled and were subjected to mastectomies.

### Surgical therapy & intra-operative margin assessment:

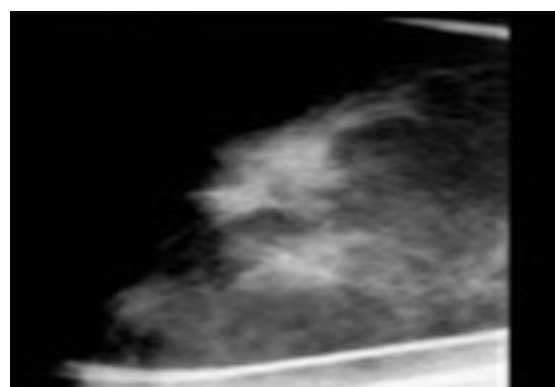
Patients underwent wide local excision including complete tumor removal with the aim of achieving grossly normal tissue margins of at least 1 cm. Localization of recurrence in the nonpalpable group (30 patients) done by fine needle aspiration guided with sonomammography in 24 patients and by open biopsy in patients diagnosed by MRI (6 patients). If surgical margins were positive or close on permanent pathology, a re-excision at a third operation or mastectomy was considered. However, whether the patient will require another operation or not is a multifactorial decision depending on the location of the close margin (i.e., whether it is a parenchymal margin vs. approaching skin or is a deep margin in a patient who had an en bloc excision of pectoralis fascia), tumor characteristics, patient's risk factors, comorbidities of the patient & cosmosis.



Figure (2): Female patient with scar of initial lumpectomy on the left breast and presented with local recurrence diagnosed on her follow up by breast U/S, MRI and confirmed by cytology.

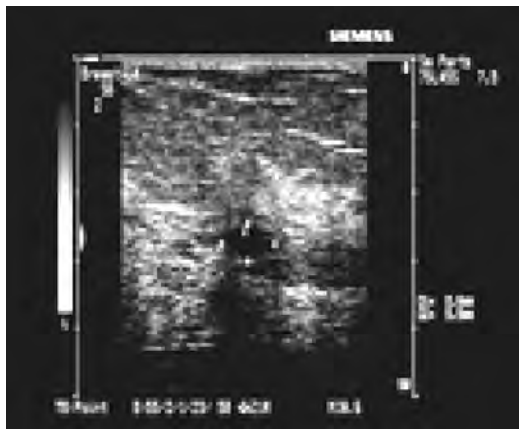


(A)

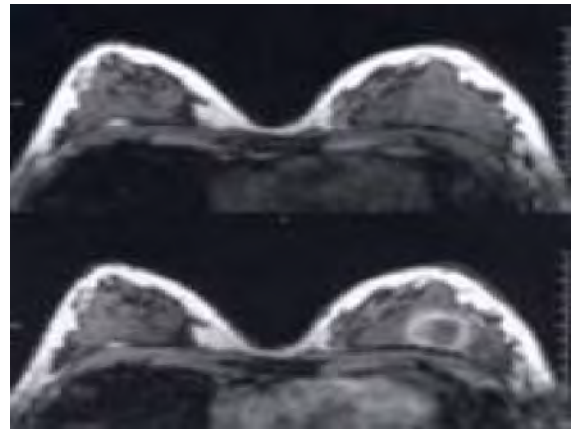


(B)

Figure (3): Mammogram shows; (A) A round mass with ill-defined margins and malignant-appearing calcifications. (B) Two irregular masses with spiculated margins (Infiltrating ductal carcinoma and ductal carcinoma in situ presented as second IBTR).

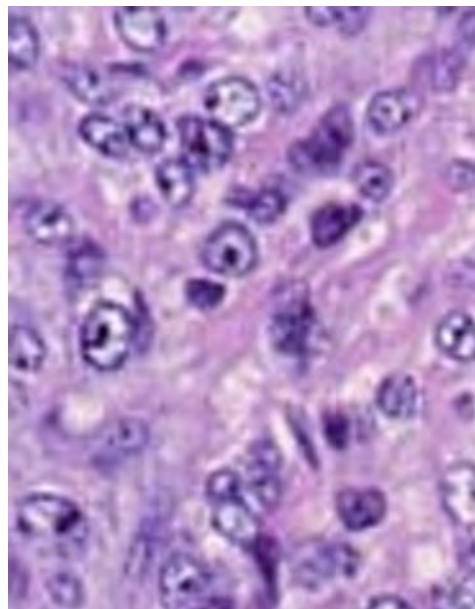


(A)



(B)

*Figure (4): (A) Ultrasound image shows nonpalpable mass within the glandular breast tissue after conservative breast surgery and presented as IBTR. (B) Breast MRI images without contrast (upper) and with contrast (lower) showing recurrent breast lump in the lower breast image on the right is highlighted by the contrast.*



*Figure (5): Papanicolaou-stained direct smear shows prominent cellular pleomorphism, mitotic figures, and absence of tubule formation. Infiltrating ductal carcinoma (poorly differentiated).*

A multisutures marking system was used to mark the superior, inferior, lateral, medial, anterior, and posterior surfaces of the resected specimen. The specimen was then sliced into 3-5mm sections perpendicular to the longest axis through the tumor mass. The sections were aligned based on the anatomic orientation, and the margins were grossly examined for proximity to the tumor mass. If the mass appeared to approach or touch a margin, an immediate re-excision of that margin was performed. If a positive margin was identified, additional tissue was excised during the same surgery, with the goal of ultimately obtaining

a negative margin. A positive margin was defined as cancer cells (invasive or ductal carcinoma in situ) touching the margin surface and a close margin was defined as cancer cells within 2 mm of the margin. A negative margin was >2 mm from cancer.

All BCS patients received adjuvant radiotherapy. As level I–II axillary lymph node dissection were performed in the previous surgery, no further axillary procedures were done. Subsequent adjuvant treatment with chemotherapy and/or endocrine therapy was prescribed as deemed necessary according to the stage of disease, hormone receptor status,



and general health of the patient. The main endpoint of the study was local recurrence in the ipsilateral breast. All patients after second surgery were subjected to median follow up by clinical examination and investigations at least every 6 months for 28 months to detect second recurrence or metastases. Mammograms were obtained at 6 months after radiation

therapy and then every year thereafter to screen for IBTR and any new contralateral cancers. A biopsy was indicated if a suspicious lesion was detected by mammography and /or sonography or if a palpable abnormality was detected on physical examination. Any carcinoma detected in the ipsilateral breast was considered an IBTR **Figure(6)**.



Figure (6): Actuarial rate of local recurrence of 58 patients at 28 months follow up.

### Results:

Median duration of follow up after re-operation was 28 (range 6-48) months **Table(1)**. The overall survival in the mastectomy group was 86.2% per cent. 4 patients died after development of systemic metastases; one after one year and the other 3 patients 21 months after mastectomy.

The overall survival in the re-excision group was 85% per cent. One patient died after 24

months due to systemic metastases and 2 patients died after 27 months from the time of re- excision. Second IBTR in the re-excision group was detected in 2 patients (10%). Chest wall recurrence in the mastectomy group was detected in one patient (3.5%). Of the 29 women who had mastectomy, 4 patients (13.8%) developed distant metastases. Of the 20 patients who had re-excision, one patient (5%) developed distant metastases **Table(2)**.

Table (1): Clinical and pathological characteristics of women with intrabreast tumour recurrence according to type of re-operation.

Clinical and pathological characteristics	Re-excision N=20	Mastectomy N=29
1) Solitary lesion	20 (100%)	5 (17.3%)
2) Multifocal lesions	0 (0)	24 (82.7%)
3) Site of recurrence :		
Skin	0 (0)	6 (20.6%)
Parenchyma	16 (80.0%)	20 (69%)
Both	4 (20.0%)	3 (10.3%)
4) Location of IBTR with reference to previous surgery:		
Scar and/or <2cm	20 (100%)	16 (55%)
Subareolar	0 (0)	6 (20%)
Other quadrant	0 (0)	7 (25%)
5) Pathological size :		
< 1 cm	6 (30%)	0 (0)
1-2 cm	14 (70%)	0 (0)
> 2cm	0 (0)	29 (100%)
6) Time from initial surgery to IBTR (years)		
< 2	3 (15%)	6 (20.6%)
2 - 3	4 (20%)	8 (27.5%)
> 3	13 (65%)	15 (51.9%)

(Values in between brackets are percentages IBTR; intrabreast tumour recurrence, N; number).

*Table (2): Data after re-operation for intrabreast tumour recurrence.*

	Re-excision N=20	Mastectomy N=29
1) Recurrence:		
- Local	2 (10%)	1 (3.5%)
- Distant metastases	1 (5%)	4 (13.8%)
2) Family history:		
- Negative	14 (70%)	21 (72.4%)
- Positive	6 (30%)	9 (27.6%)
3) Pathological nature of the first IBTR before these procedures:		
- DCIS	0 (0)	2 (6.9%)
- IFDC	16 (80%)	19 (65.5%)
- Both	4 (20%)	4 (13.7%)
- IFLC	0 (0)	4 (6.9%)
4) Progesterone receptor status:		
- Negative	5 (25%)	13 (45%)
- Positive	15 (75%)	16 (55%)
5) Overall (2years) survival	17 (85%)	25 (86.2%)

*Values in between brackets are percentages. (DCIS; duct carcinoma insitu), (IFDC; infiltrating duct carcinoma), (IFLC; infiltrating lobular carcinoma), (N; number)*

### **Discussion:**

The standard surgical approach for the treatment of intrabreast tumor recurrence of breast carcinoma is mastectomy.<sup>7</sup> The rationale for the general consensus for this recommendation is three fold: First, a second local recurrence after repeat conservative surgery is reported in approximately 10-35% of patients. Second, a second lumpectomy would yield a cosmetically unacceptable outcome. Third, re-irradiation of the whole breast after breast conserving surgery is considered inappropriate because of the likelihood of serious tissue damage.<sup>8</sup> Recently, novel brachtherapy devices and three-dimensional conformal radiation therapy techniques have brought accelerated partial breast irradiation (APBI) to the forefront as a potential treatment approach in women with intrabreast tumor recurrence of breast carcinoma.<sup>8,9</sup> However, the risk of chest wall recurrence after mastectomy for in-breast local recurrence appears to depend on whether the in-breast recurrence is primarily invasive or non-invasive.<sup>9</sup> In a study from the Joint Centre for Radiation Therapy performed in patients with non-invasive or focally invasive recurrent tumors, there were no chest wall recurrences observed at a median follow-up of 39 months.<sup>10</sup> In contrast, 7 percent of patients who presented with an invasive in-breast local recurrence

developed a subsequent chest wall recurrence.<sup>10</sup> In the present study chest wall recurrence after mastectomy for IBTR occurred in one patient (3.5%). The tumor was infiltrating duct carcinoma which is nearly similar to the results of the previous study from the Joint Centre, however the number of cases is small and duration of follow up is shorter. In a series of patients from Sweden, chest wall recurrences occurred in 19 per cent of 65 patients after mastectomy for intrabreast recurrence at a median follow up of 13 years. However, a low rate of chest wall recurrence (4 per cent) was reported by Salvadori et al.<sup>11</sup>

Survival after mastectomy for isolated in-breast local recurrence is dependent on several factors.<sup>10</sup> Recurrences that are primarily invasive are associated with worse survival than recurrences that are primarily non-invasive.<sup>11</sup> In a large multicenter study from the Netherlands, multivariate analyses of clinical and pathological factors in patients with local recurrence after breast conservation identified several factors that appeared to have an adverse impact on survival; skin involvement, extent of local recurrence > 1 cm, and positive axillary lymph node status at the time of diagnosis of the primary disease.<sup>12,13</sup> The status of the axillary lymph nodes at the initial BCT as well as at the time of the LR (local recurrence) are important prognostic

factors. Patients with negative nodes at the primary BCT have an 8% incidence of distant metastases at the LR, compared with 36% for those with 1 to 3 positive nodes, and 50% for those with 4 or more positive nodes.<sup>13</sup> These reported data agree with the incidence of our data about the LR in our patients with negative nodes at the primary BCT.

The investigator of the European Institute of Oncology in Milan reported in a non-randomised study, at a median follow up of 73 months after second surgery, that the overall survival rate at 5 years after local re-excision of IBTR was 85 per cent compared with 70 per cent for the mastectomy group.<sup>11</sup> In the present study the overall survival for the re-excision group was 85 per cent compared with 86.2 per cent in the mastectomy group at median follow up of 28 months.

In the Milan study, 19 per cent of patients treated with local excision developed a second IBTR. In comparison, 4 per cent of patients in the mastectomy group developed a chest wall recurrence.<sup>11</sup> In the present study the local recurrence in the re-excision group was 10 per cent which approximates the result in the Milan study and the chest wall recurrence in the mastectomy group was 3.5 per cent. The Milan investigators reported a big difference in risk of subsequent distant metastases; 47 per cent after mastectomy compared with 20 per cent after re-excision.<sup>11</sup> These favourable results after re-excision could simply reflect patient selection. In our study metastases developed in 13.8 per cent of mastectomy group compared with 5 per cent in the re-excision group taking in consideration smaller number of patients and shorter duration of follow up. Based on the above studies, total mastectomy does not seem to prevent patients from developing distant metastases or to prolong survival.<sup>9,11,12</sup>

Now an abundance of data exists supporting the long term safety of breast conservation therapy, consisting of BCS followed by radiation therapy, for early-stage breast cancer, most recently reported in 20 year follow-up studies.<sup>14</sup> Eligibility and exclusion criteria, established by the American College of Radiology and the American College of Surgeons are based on achievement of clear margins, ability to deliver breast radiation

therapy, and likelihood of a cosmetically acceptable outcome.<sup>13,14</sup> The inability to achieve clear margins may be a marker of excessive tumor burden in the treated breast.<sup>15</sup> It has been shown that patients with close or positive margins undergo more procedures than those with negative margins.<sup>16</sup>

Absolute contraindications to breast conservation therapy include: multicentric disease; defined as 2 or more breast cancers in different quadrants (if a satisfactory cosmetic outcome is anticipated, multicentric disease is considered to be a relative contraindication); pregnancy, persistently positive surgical margins and extensive DCIS (with or without diffuse malignant microcalcifications).<sup>17,18</sup> While relative contraindications include: multifocal disease; defined as 2 or more lesions in 1 quadrant, tumor size vs. breast size, tumor location & collagen vascular disease.<sup>17,18,19</sup> These may not only be impediments to clear margins but are also predictors of the likelihood that additional disease will be found in re-excision lumpectomy specimens.<sup>18,19</sup> In this retrospective study we did not make the distinction between extensive and contained DCIS. DCIS and IFLC make margin control difficult based on their biologic features. Our study demonstrated that when the primary tumor histology was IFDC with or without DCIS and to less extent IFLC, residual cancer was found in re-excised specimens.

Positive margins on the initial lumpectomy specimen and subsequent re-excision specimens may indicate additional tumor.<sup>20,21</sup> All patients with positive, close or undetermined margins underwent a secondary procedure in an attempt to obtain clear margins.<sup>22</sup> Of the original 58 patients requiring a second surgical procedure, 20 operated for re-excision as opposed to mastectomy. Of these 58 primary re-excision patients, 2 had persistently involved margins and therefore underwent more surgeries with residual cancer rates of 10% in the secondary re-excision specimens and 3.5% in the mastectomy specimens.

In this study, patients undergoing mastectomy as their second surgery had a significantly higher incidence of residual cancer than the re-excision group, suggesting that

these patients may have been advised to undergo a definitive procedure early on secondary to a clear indication of excessive tumor burden. However, there was no significant difference in residual cancer rates between re-excisions and mastectomies at subsequent surgeries, indicating that the presence of residual cancer after surgery is not easy to identify. The time taken for multiple re-excision attempts may not be worth the delay in administration of adjuvant therapy. While the patient ultimately should determine what an "acceptable" cosmetic result is and multiple re-excisions would likely adversely affect the aesthetic outcome.<sup>23</sup> The impact of undergoing multiple procedures versus early mastectomy (after first re-excision) on local recurrence was reported in our study as 10% versus 3.5% but this interesting topic needs to pursue in large series of patients and longer duration of follow up.

Family history has been investigated as a risk factor for failure of breast conservation therapy.<sup>24</sup> Two studies demonstrated an increased risk of second primary or new contra lateral primary cancers.<sup>24</sup> However, multiple studies also have not shown an increase in risk of local recurrence with a positive family history.<sup>24</sup> Our data did not demonstrate that patients undergoing multiple re-excisions with a positive family history of breast cancer have a significant increased risk of residual cancer. For the age factor; several studies of breast conservation therapy have found young age to be associated with increased local recurrence rates due to worse histopathologic and morphologic features.<sup>25</sup> Wazer et al demonstrated that, for positive margins, young age was an independent risk factor for finding residual tumor upon re-excision.<sup>26</sup> The current study did not show any relationship between age and residual cancer in patients undergoing more than one excision. The significance of this finding is uncertain given the small numbers and the previously documented findings.

In conclusion repeated breast conservative surgery for treatment of IBTR was not disadvantageous in selected patients. Selection should include small solitary recurrence at site of primary excision or < 2 cm in its largest

diameter, in a breast large enough to permit satisfactory cosmetic results and the resection margin must be microscopically free. They should be consented appropriately about the risk of further IBTR; however, this risk may be decreased by partial breast irradiation.

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