Salvage Mastectomy for Ipsilateral Breast Tumor Recurrence after Breast Conserving Therapy

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Abstract

Introduction: Ipsilateral breast tumor recurrence (IBTR) is one of the complications following breast conserving therapy that is conventionally treated with simple mastectomy. There is limited data evaluating the outcome after mastectomy for IBTR.

Patients and Methods: A retrospective review was conducted evaluating 176 patients operated for breast conservation during the period from January 2002 till December 2006 at the Surgical Oncology Department, National Cancer Institute, Cairo University. Thirty three patients (18.8%) experienced IBTR after breast conservation therapy (BCT). Patients with repeated lumpectomy and/or moderate disease where excluded from the study.

Results: The pathologic presentation was IDC (92.6%), ILC (3.4%), medullary carcinoma (3.4%) and mixed duct and lobular carcinoma (0.6%). The mean IBTR size was 5.0±0.91 cm. Mean follow-up after mastectomy was 61.03±12.23 months. Seven patients (21.2%) had post lumpectomy recurrence (PLR) which decreased overall survival. Ninety percent of post mastectomy recurrence occurred within the first 24 months following mastectomy.

Conclusion: Mastectomy for IBTR remains an effective treatment for most patients with risk of PMR. Strict follow-up should be routine during the first 24 months.

Key Words: Post mastectomy recurrence (PMR) — Breast Conserving therapy (BCT) — Ipsilateral breast tumor recurrence (IBTR) — MRI breast.

Introduction

THE role of breast conserving surgery (BCS) with radiation therapy (RT) in the treatment of early breast cancer has been firmly established over the past 25 years. Large randomized controlled trials have confirmed that long term survival is not impacted by the choice between initial mastectomy and BCS with RT [1-4]. Specifically, the National Surgical Adjuvant Breast and Bowel project (NSABP) B-06 trial demonstrated that the 20 year survival was equivalent for mastectomy and BCS with RT pi. Unfortunately, conservative surgery is still associated with higher rates of local recurrence in the form of IBTR compared with mastectomy [2-4].

Veronesi and his colleagues reported a cumulative 20 year incidence of local failure after BCS of 8.8% compared with a rate of 2.3% after mastectomy [3]. Studies have reported that in addition to administration of radiation therapy, younger age at lumpectomy [5-8], positive surgical margin [9-11] and clinical tumor size [12,13] are risk factors for IBTR. Recent data from the NSABP found that older age, black race, higher body mass index, larger tumors and occurrence of IBTR were all associated with higher overall mortality [13].

Outcomes after IBTR show a trend towards worse prognosis and higher rates of distant metastasis compared with recurrence-free patients [1,2,12-16]. The implications of an IBTR on distant metastasis remain a source of debate. In the original article outlining the significance of IBTR using data from NSABP B-06, Fisher and his colleagues reported that recurrence after lumpectomy increases the risk of subsequent distant metastasis by 3.41 times [2]. However, it has been argued that IBTR is not the cause of metastasis, but is instead a marker of increased risk regardless of treatment method [2,14,17].

When BCS was initially proposed, the surgical community feared the possibility of IBTR. The establishment of BCS with RT as a standard alternative to mastectomy for the treatment of most early stage breast cancer makes IBTR an important focus for research. Presently, mastectomy is the standard of care for patients with IBTR. Despite this, there is a paucity of literature regarding outcomes after mastectomy for IBTR.
Patients and Methods

A retrospective review was conducted using a prospectively-maintained database of 176 patients who underwent conservative surgery for breast cancer at the Surgical Oncology Department, National Cancer Institute (NCI), Cairo University between January 2002 and December 2006. Informed consent was obtained in all cases for the conservative surgery and for the salvage mastectomy.

Patients who underwent breast conservative surgery (BCS) and were found to have recurrent disease in the conserved breast were identified from the prospectively-maintained database for study. Thirty three Patients were identified who met these criteria (Table 1).

Exclusion criteria included initial radical mastectomy, metastatic disease at initial or IBTR presentation, contralateral breast cancer and repeated lumpectomy for IBTR.

Follow-up after conservative breast surgery:

Follow-up was performed periodically every 3 months during the first 2 years, every 4 months during the following 2 years and every 6 months during the 5th year then yearly; history, clinical examination and imaging in form of chest X-ray/± CT chest, abdomino-pelvic ultrasound/± CT abdomen & pelvis, bilateral soft tissue mammography with complementary breast ultrasound and breast MRI if needed as well as bone scan.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-recurrent patient (n=143)</th>
<th>IBTR (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years±SD)</td>
<td>52.81±10.53</td>
<td>53.85±11.53</td>
</tr>
<tr>
<td>Histology of the primary:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- IDC</td>
<td>131</td>
<td>32</td>
</tr>
<tr>
<td>- ILC</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>- Medullary</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>- Mixed duct &amp; Lobular</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mean tumor size (cm²±SD)</td>
<td>3.01±0.92</td>
<td>5.02±0.91</td>
</tr>
<tr>
<td>Axillary lymph node status:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Positive (%)</td>
<td>22/143 (15.4%)</td>
<td>33/33 (100%)</td>
</tr>
<tr>
<td>- Negative (%)</td>
<td>121/143 (84.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Adjuvant therapy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Chemotherapy alone</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>- Radiotherapy alone</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>- Hormonal treatment alone</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>- Combined line of treatment</td>
<td>143</td>
<td>16</td>
</tr>
</tbody>
</table>

Salvage mastectomy:

All surgical procedures for IBTR were done at our facility with long-term follow-up in our surgical oncology clinic. Operations for IBTR included wide local excision, simple mastectomy for recurrence, modified radical mastectomy for loco-regional failure or radical mastectomy for complex chest wall recurrence.

Adjuvant therapy:

Adjuvant therapy including RT, chemotherapy and hormonal treatment were offered when appropriate for either initial tumor, IBTR or both. Those patients with a post mastectomy recurrence (PMR) were categorized by loco-regional failure (chest wall, incision scar or axillary nodes) or distant recurrence.

Statistical analysis:

Results are expressed as mean ± standard deviation (SD) or number (%). Comparison between the mean values of different variables in the two groups was performed using unpaired student t test. Comparison between categorical data was performed using Chi square test. Correlation between different
parameters was performed using Pearson correlation coefficient. Kaplan Meier test was used for calculation of survival rate. p-value less than or equal 0.05 was considered significant and 0.01 was considered highly significant. SPSS computer program (version 12 windows) was used for data analysis.

**Results**

**Breast conservative surgery:**

There were 176 patients enrolled in the study with a mean age of 52.8±10.5 years (range between 24-77 years) at the time of breast conserving surgery (BCS).

Preoperative pathologic diagnosis was performed by fine needle aspiration cytology (FNAC) in 63 of 176 patients (35.8%), true-cut biopsy in 88 of 176 patients (50%) and lumpectomy in 25 of 176 patients (14.2%).

The tumor was in the right side in 82 of 176 patients (46.6%) and in the left side in 94 of 176 patients (53.4%). All patients underwent lumpectomy with ipsilateral complete axillary dissection.

The post-operative pathology revealed invasive ductal carcinoma in 163 of 176 patients (92.6%) invasive lobular carcinoma in 6 of 176 patients (3.4%), medullary carcinoma 6 of 176 patients (3.4%) and mixed ductal & lobular carcinoma in 1 patient (0.6%).

The mean tumor size was 3.39±1.21cm (range between 2-7cm) hence all patients were stage II breast cancer.

The tumor was grade I in 3 of 176 patients (1.7%), grade II in 167 of 176 (94.9%) and grade III in 6 of 176 patients (3.4%). The estrogen receptors (ER) and progesterone receptor (PR) status were negative in 31 of 176 patients (17.6%) and positive in 145 of 176 patients (82.4%).

The mean number of excised lymph nodes (LNs) per patient was 15.11±5.51 LNs. LNs were pathologically positive in 55 of 176 patients (31.3%) and negative in 121 of 176 patients (68.7%).

Out of the 176 patients, 162 patients had external beam radiotherapy (photon beam) 5000 cGy/25 fractions/5 weeks (200 cGy/fraction) and boost dose (electron beam) 1000-1600 cGy/5-8 fractions/1-1.5 week (200 cGy/fraction). Post operative chemotherapy was given in the form of anthracycline containing regimen with or without taxanes to 171 of 176 patients (97.2%) and hormonal treatment was given to 161 of 176 patients (91.5%).

**Ipsilateral breast tumor recurrence:**

Thirty three patients developed ipsilateral breast tumor recurrence (IBTR); the mean time from BCS to IBTR was 14.03±7.6 months.

IBTR was detected during the follow-up period by self examination in 7 of 33 patients (21.2%), clinical examination in 7 of 33 patients (21.2%), and soft tissue mammography and/or magnetic resonance imaging in 19 of 33 (57.5%) (Case 1 and Case 2).

Pathologic confirmation was performed by FNAC in 9 of 33 patients (27.3%), true-cut biopsy in 15 of 33 patients (45.4%) and lumpectomy with frozen section in 9 of 33 patients (27.3%).

Metastatic work up was negative for all patients, as previously described in the follow-up period. Salvage mastectomy for IBTR was performed for this group of patients after full informed consent.

**Follow-up after salvage mastectomy:**

The mean follow-up after salvage mastectomy was 61.03±12.23 months. Twenty five patients were salvaged till the end of the study. Seven of 33 patients (21.2%) developed local recurrence, and 8 of 33 patients (24.2%) developed distant metastases.

Seven of 8 patients (87.5%) with distant metastases had concomitant local recurrence. Metastasis occurred in the bones (3 out of 8 patients, 37.5%), in the liver (1 out of 8 patients, 12.5%), in the lungs (1 out of 8 patients, 12.5%), in the brain (2 out of 8 patients, 25%), and 1 (12.5%) patient had multiple bone, lung, and brain metastases.

Local recurrence was at the chest wall or incision scar in 6 of the 7 patients (85.7%) and 1 of the 7 patients (14.3%) at the interpectoral lymph node (Rotter’s node).

Local recurrence was found via self examination in 3 patients (42.9%) and via the clinical examination in 4 of the 7 patients (57.1%). Compared with IBTR presentation, local recurrence after mastectomy for IBTR was more likely to be found by clinical examination (p=0.01).

About ninety percent of PMR occurred within the first 24 months following salvage mastectomy (eighty five percent if the sole multiple metastatic patient was excluded).

The mean time to PMR was 19.71±5.25 months while that to distant metastases was 35.29±15.44 months. Most patients with local failure after mastectomy for IBTR had wide local excision and adjuvant therapy as shown in (Table 2).
Case (1): Female patient 55 years old did conservative right breast surgery three years before, pathology was invasive duct carcinoma. (a): Right soft tissue mammography shows an ill-defined opacity and micro calcification (arrowed) warranting further MRI evaluation. (b,c,d): Axial T1W1, axial T1W1 with fat suppression, and sagittal T1W1 with subtraction depicted the speculated lesion at the operative bed (arrowed). (e): Dynamic post contrast show the malignant pattern of lesion enhancement. (f,g,h): Post-contrast images with fat suppression. (i): Post contrast with fat suppression.
Salvage Mastectomy for Ipsilateral Breast Tumor Recurrence

Case (2): Female patient 82 years old did conservative right breast surgery two years before, pathology was invasive duct carcinoma. (A1,A2): Bilateral soft tissue mammography shows operative bed non specific opacity and left suspicious opacity warranting further MRI evaluation. (B1,B2): Axial T1WI and axial T2WI. (C1,C2): Sagittal T1WI with subtraction depicted the speculated lesion at the operative bed and in the left breast (arrowed). (D1,D2): Dynamic post contrast series show the malignant pattern of lesion enhancement. (E1,E2): Post contrast images with fat suppression corresponding to the dynamic images. (F1,F2): Post contrast subtracted images.

Table (2): Clinical characteristics and treatment of post mastectomy recurrence (PMR).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Post Mastectomy Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Local recurrence</td>
</tr>
<tr>
<td>Patients number</td>
<td>7</td>
</tr>
<tr>
<td>Site</td>
<td>6 Chest wall</td>
</tr>
<tr>
<td></td>
<td>1 Interpectoral node</td>
</tr>
<tr>
<td></td>
<td>3 Bone</td>
</tr>
<tr>
<td></td>
<td>1 Multiple</td>
</tr>
<tr>
<td>Surgery:</td>
<td></td>
</tr>
<tr>
<td>- Wide local excision</td>
<td>5</td>
</tr>
<tr>
<td>- Radical mastectomy</td>
<td>1</td>
</tr>
<tr>
<td>- None</td>
<td>1</td>
</tr>
<tr>
<td>Adjuvant therapy:</td>
<td></td>
</tr>
<tr>
<td>- Chemotherapy alone</td>
<td>0</td>
</tr>
<tr>
<td>- Radiotherapy alone</td>
<td>0</td>
</tr>
<tr>
<td>- Hormonal treatment alone</td>
<td>1</td>
</tr>
<tr>
<td>- Combined treatment</td>
<td>6</td>
</tr>
</tbody>
</table>

Discussion

Multiple studies have identified risk factors for IBTR including: Tumor size, young age, favorable tumor markers, high proliferative index, lymphovascular invasion, positive surgical margin, and omission of RT [12,13,15,16,18-22]. There is a paucity of data on time to IBTR after BCS as a risk factor for PMR, but our data revealed no impact of time to IBTR. The adverse relationship between IBTR and survival is established [12,12-16] and our study demonstrates that PMR, whether locoregional or distant, further decreases survival (p=0.01). The presence of recurrent cancer after mastectomy is an unfortunate and ominous sign. Whether IBTR and PMR are the result of inadequate BCS, poor host-tumor relationship, or inadequate adjuvant treatment is still debated. Regardless of mechanism, physicians should recognize the impact of the IBTR, and particularly PMR, on the patient and the progression/prognosis of disease.

Our study group had a PMR locoregional recurrence rate of 21.2%, with an additional 3% experiencing distant metastases, for a total recurrence rate of 24.2%. Previous studies have reported post mastectomy local failure rates of approximately 10 percent [23-25], which is similar to our results. Although mastectomy is the standard therapy for IBTR, it does not eliminate the risk of subsequent local and distant relapses [21,23-27]. Our data suggests that clinicians should encourage regular follow-up visits for IBTR patients. About ninety percent of PMRs occurred within 24 months of mastectomy, and these recurrences were often discovered during follow-up period. In fact, period of PMRs were found by clinical examination compared with just of IBTRs (p=0.01). Imaging was important during both IBTR and PMR presentations, but was only used when clinically relevant after mastectomy (e.g., palpable mass or chest pain) because mammograms of the mastectomy scar were not obtained. Other studies have reported poorer predicted overall survival in patients whose recurrence was found during physical examination [23]. We continue to suggest routine breast/chest wall self examination and scheduled physician examination after mastectomy for IBTR.
Our data confirms the overall relationship between larger IBTR tumor size and increased risk of subsequent PMR, including both locoregional and distant failures. Of our patients with PMR had IBTR tumors \( >2 \text{cm} \) (T2 or larger), compared with the non PMR patients \( (p=0.006) \). A review of existing literature revealed little data regarding the impact of IBTR tumor size upon later PMR. A recent study of outcomes after repeat BCS found that IBTR tumor size \( >2 \text{cm} \) negatively affected local disease-free survival, with a hazard ratio of 2.8 compared with smaller tumors \[22\]. Nodal failure was not observed in our study.

Although the role of RT in BCS is well established \[1-4,28\], adjuvant therapy after IBTR and/or subsequent PMR is still debated. Almost all of our patients received RT after lumpectomy, which is consistent with current standard of care, but only 12% of patients underwent post mastectomy RT. For whom, this was their second course of RT after initial treatment with BCS. Although it is clear that RT is an essential part of BCS \[1-4,28\], the utility of a second course of RT for IBTR or PMR has been suggested to be contraindicated due to the risk of toxicity to surrounding structures and poor cosmetic results \[29\]. However, with approximately 10 percent of breast cancer survivors experiencing IBTR and more evidence suggesting that partial breast irradiation is safe and effective after lumpectomy, there may be a role for second BCS with RT in a select group of IBTR patients \[30-33\]. The European institute of oncology in Milan, Italy has reported on second lumpectomy for the treatment of IBTR. Using retrospective data, this group reported that IBTR tumor \( <2 \text{cm} \) and times to IBTR >48 months were positive factors when considering second lumpectomy \[22\]. Presently, there is a Radiation Therapy Oncology Group phase II trial investigating repeat lumpectomy and partial breast RT in patients who underwent initial lumpectomy and whole-breast RT. With results from studies such as this, further understanding of breast cancer biology, and more targeted radiation techniques, there may be opportunities to individualize treatment options and offer women a second chance at BCS with re-irradiation \[29\].

Similarly, few patients received post mastectomy chemotherapy. In our study, 66.6% of women received hormonal therapy as indicated by hormone receptor status after IBRT, but only 18% received post mastectomy adjuvant chemotherapy. There is limited data to support or refute the use of chemotherapy in this patients group. The BIG 1-02/IBCSG 27-02/NSABP-B37 trial, a randomized phase III trial, is investigating the effectiveness of adjuvant chemotherapy in treating women who have undergone re-therapy in treating women who have undergone resection for local and/or regional relapsed breast cancer; hopefully the results will define the role of chemotherapy in this setting.

We recognize the limitations of this study. First, our study had 33 patients with IBTR is relatively small, and dividing that group based on outcome after IBTR further decreases statistical power. Despite the limitation of size, our outcomes show that the risk of PMR is related to IBTR tumor size and dramatically impacts survival. Second, this trial precluded analysis of accurate standardized information on surgical margin width (although all specimens had tumor-free margins). Studies have shown that positive margins and close negative margins are associated with an increased risk of IBTR \[34\]. Third, we did not differentiate between true recurrence (TR) and new primary tumor (NPT). Although there is no universal classification system, several studies have differentiated TR from NPT based on tumor histology and location within the breast. These reports suggest differences between the two regarding tumor behavior, recurrence, and outcomes. It has been suggested that TR has a worse prognosis than an NPT \[26,35,36\]. Classifying IBTR into these distinct entities may help in understanding the complicated behavior of IBTR.

**Conclusion:**

Mastectomy for IBTR remains effective treatment for most patients and affords reasonable local control. Monitoring patients for the development of an IBTR may be aided by computerized models \[37,38\], but locoregional failure and distant metastasis remain significant problems and should be a focus of the follow-up examinations.

Clinicians should be particularly concerned about patients with IBTR tumors which are \( >2 \text{cm} \) due to the increased risk of subsequent recurrence after mastectomy. Strict post-mastectomy follow-up care and thorough clinical examination should be routine, especially during the first 24 months after salvage mastectomy for IBTR. Furthermore, such a recurrence dramatically decreases survival when compared with IBTR alone. Aggressive surgical and adjuvant treatment may prolong survival in this setting.

We hope that trials evaluating outcomes after IBTR will better define potential roles for adjuvant therapies and yield a greater understanding of risk factors, prevention, and treatment.
References


