Image-Guided Breast Conserving Surgery

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KEYWORDS

Breast Cancer – Image -Guided – Surgical Margin – Palpation-Guided – Breast-Conserving – Frozen – Cosmetic Outcome.

ABSTRACT

Background: Breast-conserving surgery (BCS) has gained wide acceptance as the treatment of choice for early-stage breast cancer. One of the primary goals of BCS is to obtain tumor-free resection margins. In practice, the excision of a palpable breast carcinoma is guided by preoperative diagnostic images and the intraoperative tactile skills of the surgeon. The somewhat 'blind' approach of using palpation-guided surgery is known to be highly inaccurate, with studies worldwide reporting positive resection margins in up to 41% of patients. In recent years, ultrasonography has emerged as an effective guidance tool during surgery and ultrasound-guided surgery has been introduced into breast cancer surgery as a method of excising nonpalpable breast cancer. **Objective:** The aim of this study is comparing ultrasound-guided vs palpation-guided conservative breast surgery in obtaining tumor-free resection margins. **Methods:** This study was a prospective randomized controlled clinical trial where patients with early breast cancer (T1-T2) and eligible for breast conserving surgery are randomly assigned (1:1) into two arms. **Arm A:** included the patients who will undergo ultrasound-guided breast conserving surgery. **Arm B:** included the patients who will undergo the conventional palpation-guided breast conserving surgery. **Results:** Overall, 142 patients undergoing breast conserving surgery were enrolled: 71 were allocated to the Ultrasound-guided (US) group (Arm A) and 71 to the Palpation-guided (PG) group (Arm B). Patient and tumor characteristics were comparable between the two groups. Age, Body mass index, tumor laterality, tumor location and tumor stage were comparable in both groups and statistically insignificant. Despite that the final tumor size was comparable between both groups, IOUS significantly reduced the main specimen volume and the least negative margin width ($p<0.001$). The median operative time was significantly longer in the US group bey around 27 min than in the PG group and this was statistically significant in favor of the PG surgery ($p<0.001$). The involved resection margin rate was significantly higher in the PG group and thus the need for reoperation ($p<0.001$). **Conclusion:** IOUS is the only method allowing a true real-time visualization and continuous control of resection margins during all phases of BCS. In our single-institution study, IOUS demonstrated clear superiority over palpation-guided surgery in both oncological and surgical outcomes except for the operative time (smaller excision volume yet, with optimum resection margins). IOUs provides much better tumor localization in small breasts with dense fibroadenosis. Since all the other available localization techniques (including palpation) limit the surgeon's visual guidance during BCS, IOUS could be regarded as one of the most significant modern technological innovations in the field of breast cancer surgery, restoring sight to the breast surgeon. Our findings strongly suggests that the integration of IOUS in breast conserving surgery could be regarded as a highly beneficial surgical approach.

1. Introduction

Breast-conserving surgery (BCS) has gained wide acceptance as the treatment of choice for early-stage breast cancer. One of the primary goals of BCS is to obtain tumor-free resection margins. Positive or focally positive margins for tumor cells are associated with an increased risk of local recurrence, and in case of tumor-positive margins, re-excision or even mastectomy are often required to achieve negative margins. (1,2,3,4)

In practice, the excision of a palpable breast carcinoma is guided by pre-operative imaging and the intraoperative tactile skills of the surgeon. The somewhat 'blind' approach of using palpation-guided surgery is known to be highly inaccurate, with studies worldwide reporting positive resection margins in up to 41% of patients. (4,5,6,7)

High-frequency real-time ultrasonography was introduced in the 1970's and the technology has steadily improved, resulting in increased sensitivity, greater portability and the availability of ultrasonography in the operation theatre. In recent years, ultrasonography has emerged as an effective guidance tool during surgery and it has been introduced into breast cancer surgery as a method of excising nonpalpable breast cancer. (8,9,10,11)

Considering the advantages when applied to nonpalpable masses, ultrasound-guided surgery for palpable breast cancer should similarly decrease margin positivity and excision volumes.

The following study is a randomized controlled study aiming to compare the effectiveness of ultrasound-guided surgery in palpable breast cancer with the standard palpation-guided surgery in obtaining tumor free resection margins.

2. Patients and Methods

This study was a prospective randomized controlled study conducted at the National Cancer Institute, Cairo University between January 2019 till January 2021. The protocol was approved by the local Ethics Committee and all the patients provided informed consent.

Inclusion and Exclusion Criteria:

Female patients diagnosed with T1-T2 palpable invasive breast cancer and deemed suitable for breast conserving surgery were enrolled.

Male patients, patients with multicentric or multifocal tumors, inflammatory breast cancer, previous breast conserving surgery, as well as patients who were candidates for mastectomy, were excluded. Patients who received neoadjuvant chemotherapy were also excluded.

Study Characteristics

Eligible participants (142 patients) were randomly assigned using the toss technique to either arm A (Ultrasound-guided surgery) or arm B (Palpation-guided surgery) in a 1:1 ratio, generating two homogeneous groups.

Ultrasound-guided surgery (Arm A)

On the day of surgery, in the pre-anasthesia room, we performed an ultrasound (US) scan of the targeted lesion to accurately localize the tumor (black circle) and a 1-cm safety margin (red dotted circle) (Figure 1). In the Operation theatre, the ultrasound probe is covered in sterile drapes. After the skin incision, we used the US probe to define the safety margins of the tumor for safe resection (namely: cranial, caudal, medial, lateral and superficial if the skin is not excised). (Figure 2).

We performed a wide local excision of the tumor with continuous visualization of all the resection margins using the US in real time. Then after the excision, an ex-vivo US examination of the specimen is done to confirm the resection margin width is sufficient (Figure 3).

The specimen is then oriented with the following threads (short thread denoting the superior margin, long thread denoting the lateral margin and double short threads denoting the superficial margin if the skin wasn't excised) (Figure 3) and the specimen is sent to the pathologist for frozen sectioning of the margins.

Associated axillary lymph nodes were surgically addressed in the form of either Sentinel lymph node biopsy (SLNB) or axillary lymph node dissection of level I and II. Drains were used only when needed.

Palpation-guided surgery (Arm B)

Patients in this group underwent breast conserving surgery using the conventional palpation-guided technique. Tumor resection was guided by palpation in the standard manner where the fingers were used to palpate the tumor, retract it and guide the dissection. The adequacy of the resection using this approach relied on the experience and tactile abilities of the surgeon, and no objective imaging during the surgery was used.

Histologic Characteristics and Volume Calculations

All specimens were sent for frozen sectioning for assessment of margins. The presence of invasive tumor or Ductal carcinoma insitu (DCIS) in the margins was documented and dealt with immediately at the same sitting. The fresh specimen volume was calculated as a volume of a rhombic prism, using the formula $V=d1*d2*h/2$, where d1,d2 and h are the diameters of the main specimen.

The closest margin width was calculated as the minimal distance between the tumor and the closest resection margin. Reoperation was recommended for any resection margin involvement with DCIS or the presence of "ink on tumor" for the invasive component.

Figure 1 Tumor localization

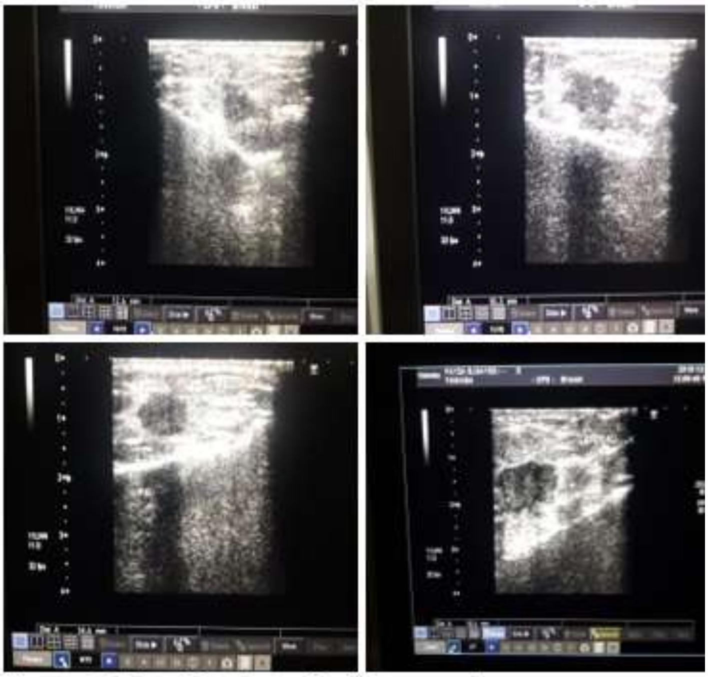

Figure 2 Identification of safety margins

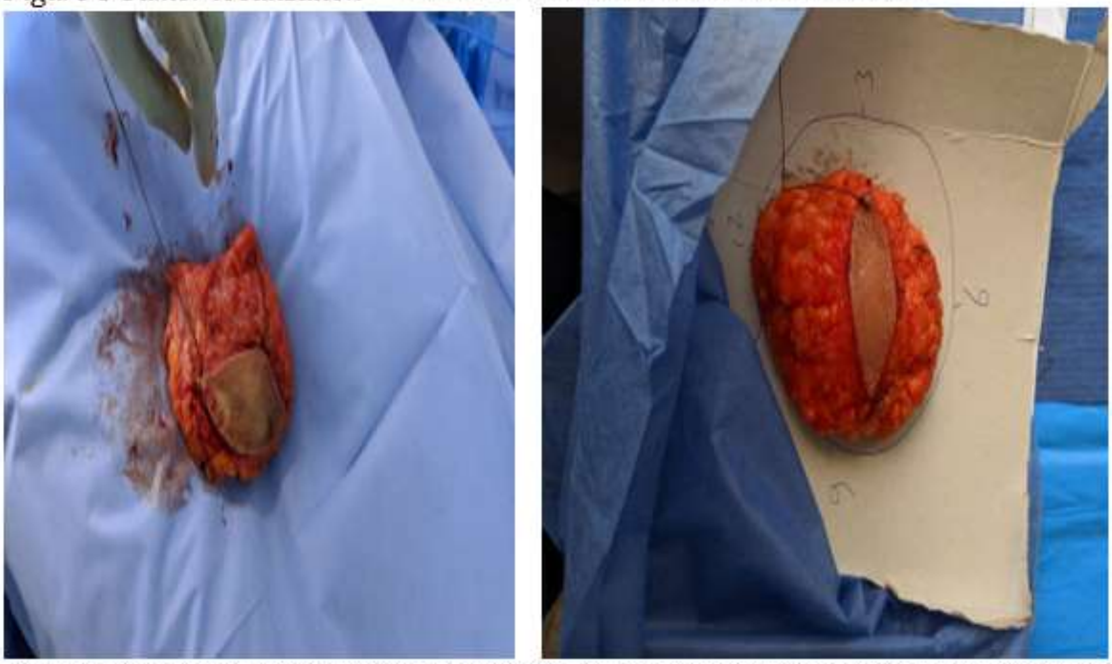

Figure 3 Specimen orientation post excision for frozen sectioning and ex-vivo imaging

3. Results

Overall, 142 patients undergoing breast conserving surgery were enrolled: 71 were allocated to the Ultrasound-guided (US) group (Arm A) and 71 to the Palpation-guided (PG) group (Arm B).

Patient and tumor characteristics were comparable between the two groups. (Table 1). All patients were females, and the mean age was 51 in the US group and 53 in the PG group. The Body Mass Index (BMI) results were also comparable between both groups ranging between 19-41 kg/m2 in the US group and 20-44 kg/m2 in the PG group. More than half the patients in both groups had a bra cup size of B (67% in USG and 70 % in PG). Most patients came with left sided breast cancer (60% in USG and 56% in PG). The upper outer quadrant tumor localization accounted for nearly half of all cases in both groups (42.3% in the US group and 49.3% in the PG group) and the central quadrant tumor localization accounted for the least percentage (5.6% in the US group and 7% in the PG group). Pathological T1 was reported in 44% of tumors in US group and 31% in PG group. All these parameters were comparable between both groups and differences were statistically insignificant.

Table 1: Patient and tumor characteristics

	Arm A (n=71)	Arm B (n=71)	P value
Age (years)	51 (32. -75.)	53 (31 -76)	
Body-mass index (kg/m^2)	26 (19-41)	27 (20-44)	0.7
Laterality			
Right	28 (39.4%)	31 (43.7%)	0.609
Left	43 (60.6%)	40 (56.3%)	
Tumor Stage			
T1	31 (43.7%)	22 (31.0%)	0.118
T2	40 (56.3%)	49 (69.0%)	
Cup Size			
A	17 (23.9%)	8 (11.3%))	
B	48 (67.6%)	50 (70.4%)	0.053
C	6 (8.5%)	13 (18.3%)	
Quadrant			
UOQ	30 (42.3%)	35 (49.3%)	
UIQ	11 (15.5%)	10 (14.1%)	
LOQ	16 (22.5%)	14 (19.7%)	0.741
LIQ	10 (14.1%)	7 (9.9%)	
Central	4 (5.6%)	5 (7.0%)	

Data are presented as number (%) or mean (SD, Range). *: significant as P value <0.05

Surgical and Oncological outcomes

Surgical and oncological outcomes, according to the surgical approach (USG or PG), are shown in [Table **2** and

Table 3]. IOUS always guaranteed an accurate localization of the targeted lesion and Wide Local Excision (WLE) was successfully completed via US guidance in all cases. Tumor histologic types were homogeneously distributed among both groups, with Invasive Duct Carcinoma with DCIS component being the most represented (48% in the US group and 46.5% in the PG group). Despite that the final tumor size was comparable between both groups (2.19 ± 0.59 in the US group vs 2.71 ± 0.75 in the PG group), IOUS significantly reduced the main specimen volume (mean volume of 70 cm3 (ranging from 14-126) in the US group vs a mean volume of 170 cm3 (range: 26.5-315) in the PG group; p<0.001) (

Table 3). Also, the least margin width was statistically significant among both groups with a mean of 1.35 cm (range: 0.3-2.1) in the IOUS group vs a mean of 3.7 cm (range: 0.2-7); p<0.001. Median excision time was 27 minutes shorter in the PG group (mean: 60.35 min (range: 45-75) compared to a mean of 87.54 min (range: 70-115) with IOUS; p<0.001). IOUS significantly reduced the resection margins, with a least margin width of 1.35 cm (range: 0.3-2.1) compared to 3.7 cm (range: 0.2-7) in the PG group; p<0.001). The involved resection margin rate was significantly higher in the PG group 19.7% compared to 7% with IOUS; p=0.046. Four of the 5 cases with involved margins in the US group were due to an unexpected finding of a DCIS component (80%) and the last case was due to an invasive tumor involvement of the margin; among the 14 cases with involved margins in the PG group, 9 (64%) were due to a DCIS component and the remaining 5 cases (36%) were due to an invasive component. All the 5 patients (7%) with involved margins in the US group underwent re-excision. Mastectomy was needed due to frequently positive margins for 3 out of the 14 (4.2%) patients in the PG group, while the remaining 11 (15.5%) patients underwent only surgical margin clearance. (Table **2**).

Table 2: Margin Status

	Arm A (n=71)	Arm B (n=71)	P value
Margin Status			
Positive	5 (7.0%)	14 (19.7%)	
- **IDC**	1 (1.4%)	5 (7%)	0.046*
- **DCIS**	4 (5.6%)	9 (12.7%)	
Negative	66 (93.0%)	57 (80.3%)	
Additional Treatment	5 (7%)	14 (19.7%)	
Re-excision	5 (7%)	11 (15.5%)	
Mastectomy	0	3 (4.2%)	

Least free margin (cm)	1.35 (0.3-2.1)	3.7 (0.2-7)	<0.001*

Data are presented as number (%) or mean (SD, Range). *: significant as P value <0.05

Table 3: Post-operative surgical measurements

	Arm A (n=71)	Arm B (n=71)	P value
Fresh Specimen Volume (cm^3)	70 (14-126)	170 (26.25-315)	<0.001*
Final Size of the mass (cm)	2.19 (1.5-3)	2.71 (1.95-3.4)	0.45
Grade			
1	9 (12.7%)	4 (5.6%)	
2	57 (80.3%)	63 (88.7%)	
3	5 (7.0%)	4 (5.6%)	
Final Histology			
IDC	30 (42.2%)	33 (46.5%)	
IDC + DCIS	34 (48%)	33 (46.5%)	
ILC	2 (2.8%)	2 (2.8%)	
Others	5 (7.0%)	3 (4.2%)	

Data are presented as number (%) or mean (SD, Range). *: significant as P value <0.05

4. Discussions

Margin status and second surgeries:

Intraoperative Ultrasound (IOUS) guarantees an objectively measured control of resection margins during breast conservative surgery for palpable tumors, whereas palpation guided surgery relies on the subjective approximation of the desired distance from the tumor.

In our study, we observed a lower rate of involved margins in the IOUS group compared to the PG group for palpable lesions (7% compared to 19.7%; p=0.046) and this difference was statistically significant. Four of the five patients that had involved margins were DCIS and only one case showed invasive carcinoma infiltrating the margins. All the 5 cases were treated with re-excision to attain tumor free margins.

Many other studies showed the same advantages for using IOUS. The COBALT trial demonstrated a significant reduction in involved margin rates for palpable tumors with IOUS compared with Palpation-guided surgery (3% vs 17%; p=0.009). Similarly, a retrospective review [(7)] reported a significantly lower likelihood of margin involvement with IOUS compared with Palpation-guided surgery (9% vs 42%; p=0.01) and a lower re-excision rate (9% vs 34%; p=0.04). Eggeman et al. [(13)] also reported a significant reduction in reoperation rates for positive margins with IOUS compared with PG surgery (11.6 % vs 24,1%; p=0.004).

Eichler[(14)] and his associate agreed with our findings, as negative margins were obtained in 96.4% in US group, compared to 82.5% in the PG group, with a significant difference between them (p<0.05). Moore et al. also reported that only one patient (3.5%) in the IOUS group had infiltrated margins, compared to seven patients (29%) in the PG group, with a significant difference in statistical analysis (p<0.05). Krekel et al. also noticed a significant decline in resection margin involvement with IOUS application (p=0.009). Infiltrated margins were encountered in 3% in the IOUS group and 17% in the PG group.

Surgical Volume excision

Our study confirmed that IOUS reduces the volume of the surgical specimen resecting less healthy breast tissue. Moreover, this reduction does not affect the rate of complete excision of the tumor and nor does it have an impact on local recurrence rates. Volume excised is a surrogate marker for the cosmetic outcome. Our data shows that US-guided lumpectomy achieved good margins with a much smaller volume of resection compared with palpation-guided surgery (mean resection volume: 70 cm3 (range:14-126) compared to 170 cm3 (range: 26.25-315); p<0.001).

The same finding was reported by many other authors. Moore et al. found that the volume of the lumpectomy specimen for palpable infiltrating ductal carcinomas was smaller in their US-guided group (104 cm^3) compared to their palpation-guided group (114 cm^3), with increased mean clear margin width (7.6 versus 4.8 mm, respectively). Also, Krekel et al. reported that US-guided surgery resulted in smaller excision volumes compared to palpation-guided surgery in palpable breast cancer patients (38 versus 57 cm^3; $p = 0.002$). Larger excisions may lead to less margin positivity but may end up with poor cosmesis. Karanlik and his associates found also that US-guided lumpectomy achieved good margins with a much smaller volume of resection compared with palpation-guided surgery (mean resection volume, 89.9 versus 108.1 cm^3, respectively, $p = 0.048$).

Operative time

In our study, the median IOUS excision was around 27 min longer than PG surgery with an average of 87.54 min (range: 70 - 115) in IOUS group vs 60.35 min (range: 45-75) in PG group; P<0.001) and it was statistically significant.

Massimo F. et al., reported a median IOUS excision time of only 7 min longer than PG surgery. The Cobalt trial [(12)] reported also shorter excision times between IOUS group and PG group, describing an additional 5-min operative time needed for IOUS before and after the procedure.

The longer time reported in our study is due to the delay in the setting of the IOUS as it is a novel technique in our institute, and probable because we are not yet accustomed to it. With practice and increasing number of cases operated with IOUS, our timing will hopefully approach that of the other reported studies.

5. Conclusion

IOUS is the only method allowing true real-time visualization and continuous control of resection margins during all phases of BCS. In our single-institution study, IOUS demonstrated clear superiority over palpation-guided surgery in both oncological and surgical outcomes except for the operative time (smaller excision volume yet, with optimum resection margins). IOUs provides much better tumor localization in small breasts with dense fibroadenosis. Since all the other available localization techniques (including palpation) limit the surgeon's visual guidance during BCS, IOUS could be regarded as one of the most significant modern technological innovations in the field of breast cancer surgery, restoring sight to the breast surgeon. Our findings strongly suggest that the integration of IOUS in breast conserving surgery could be regarded as a highly beneficial surgical approach.

Limitation

This study has some limitations. First, the study was based on a single institution experience, which may limit the generalizability if the findings. Additionally, the study population is not wide even though the study groups were homogenous. We did not conduct a specific cost-benefit analysis to evaluate the cost-saving potential of IOUS, the cost of the apparatus and its maintenance should be compared to the cost of repeat surgery in case of involved margins. The performance of IOUS may be limited in cases of pure DCIS and invasive lobular carcinoma, as assessing the boundaries of these lesions by US is often challenging.

Recommendations

We recommend a larger sample size with multicenter cooperation to validate the results. Further research is recommended to generalize the results.

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