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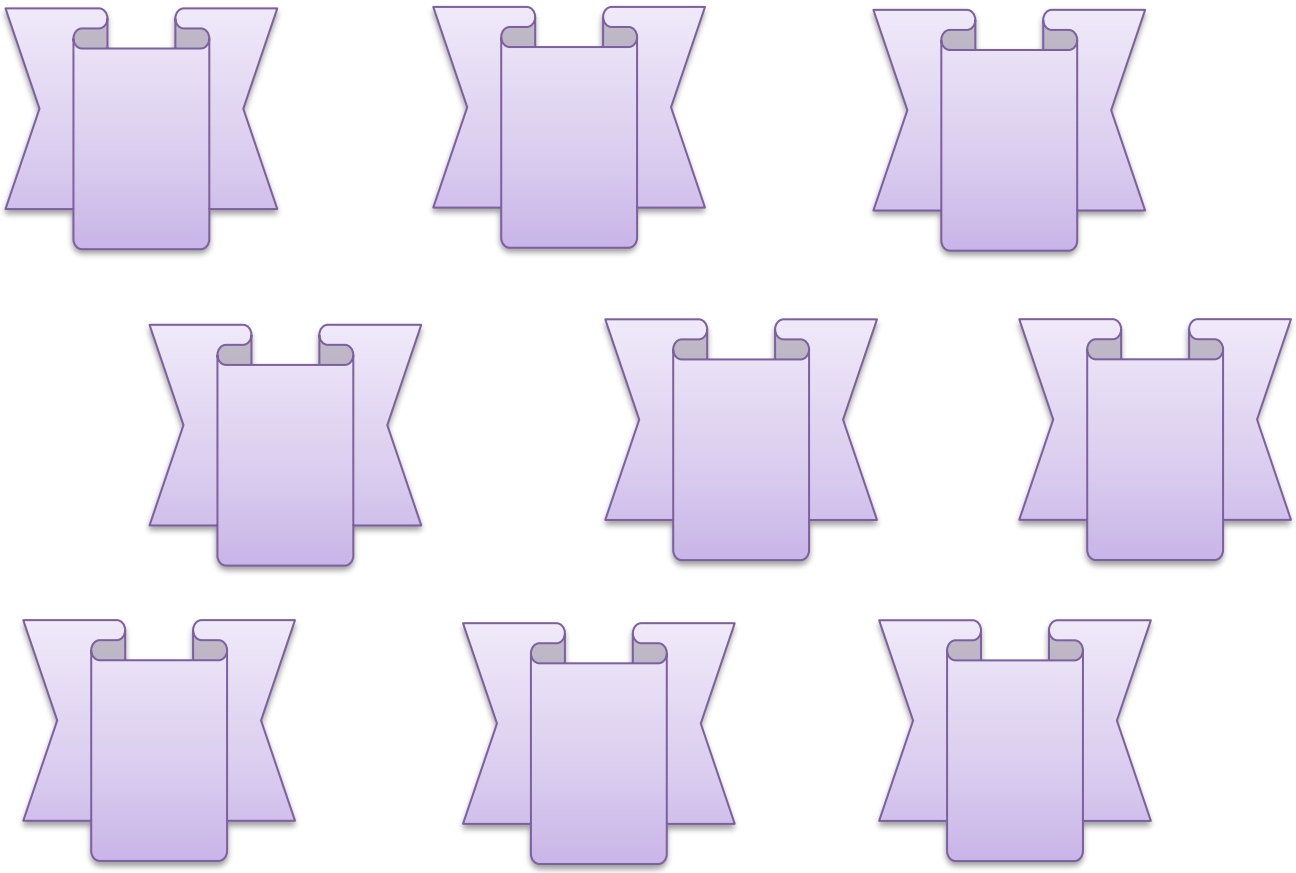

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Original Article

Comparative Study between Intraoperative Ultrasound and Frozen Section in the Assessment of Margins in Conservative Breast Surgery

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ABSTRACT

Background: Frozen sections [FS] analysis is the most often used intraoperative method for analyzing excisions of breast tumors. However, ultrasound may play a pivotal role and avoids the invasiveness.

Aim of the Study: The work's objective was to compare the use of FS versus intraoperative ultrasound [IOUS] in determining an appropriate negative margin for conservative breast surgery

Patients and Methods: With the same inclusion and exclusion criteria, we included 30 patients who were divided into two equal groups, the first for FS and marked as [Group-A], and the second group for IOUS and marked as [Group-B]. Results of FZ and IOUS were compared to the results of histopathology. In addition, the operative time, volumetric resection and short-term recurrence were document.

Results: The FZ group had a significantly larger mean value of safety margins than the IOUS group, while the pathological group had the lowest mean value. The FZ had a sensitivity of 80%, specificity of 100%, accuracy of 86.7%, positive predictive value [PPV] of 100%, negative predictive value [NPV] of 71.4%, and Kappa agreement of 0.727 [0.389-1.00], with a p-value < 0.05 indicating statistical significance. Moreover, the IOUS group's sensitivity, specificity, accuracy, PPV, and NPV were all 100%. Their Kappa agreement was 1.00 [1.00-1.00], and their p-value [p<0.05] indicated statistical significance.

Conclusion: When evaluating safety margins in conservative breast surgery, intraoperative ultrasound performs better than frozen sections.

Keywords: Intraoperative; Ultrasound; Frozen Sections; Breast Surgery.

INTRODUCTION

Breast cancer is the commonest cancer affecting women worldwide. In Europe, for example, 430,000 new cases are reported annually [1]. The widespread use of the screening programs and methods, there is an increase of early detection of smaller, non-palpable invasive breast cancers [IBC], and ductal carcinoma in situ [DCIS]. Both are responsible for up to 20% of newly diagnosed primary breast cancer cases [2].

Surgery is the standard and first line treatment option for early-stage breast cancer. However, breast conserving surgery [BCS] plus radiation therapy is widely accepted as an alternative as it is equally safe as mastectomy. This progress, together with the use of intra-operative radiation therapy [IORT], the introduction of skin/nipple sparing methods, and the oncoplastic repair of huge surgical defects, has led to the need for intraoperative information regarding the margin status [3].

Studies suggested that to achieve clear margins, 20–25% of patients submitted to BCT may need a second intervention. Others suggested that this number is as high as 72%. The optimal surgical margin distance varies between and within countries. However, the recommended minimum margin width is accepted to be between 2 and 10 mm [4].

Although BCT is the recommended surgical manoeuvre for patients who are not at high risk, the surgeon must precisely assess the disease extent and margin condition during surgery to reduce the likelihood of the need for a second procedure. This could be achieved with a technological aid that provides precise intraoperative information on the margin status and confirms removal of the cancerous tissues [5]. For this purpose, an intraoperative margin assessment [IMA] approach was suggested [6].

The problem of BCS is removing the primary tumour with well-defined [negative] margins. Factors that affect the negative-margin rate after the initial surgery include cell type, tumour size, lymphovascular invasion [LVI], multifocality, and excision volumes. Thus, margin status functions as a predictor of in-breast recurrence [IBR] and has a local correlation with disease control [7].

The need for a re-excision intervention is due to a positive margin, which may be associated with unwanted consequences [e.g., poor cosmetic outcome, prolonged wound healing, infection, increased costs, patient anxiety, and possibly noncompliance with the re-excision recommendation]. The rate of re-excision procedure for DCIS alone have varied from 31% to 46%, and for DCIS with IBC, varied from 11% to 46% [8].

The characterization of a suitable histological border of excision has been the subject of much debate. All the same, tumour-localizing techniques have been introduced, such as guide-wire localization [GWL], radio-guided occult lesion localization [ROLL], intraoperative ultrasound [IOUS], and single-photon emission computed tomography [SPECT]. These techniques include direct excision, but they only have a "macroscopic" impact on the cancer cells that are close to the margins [9].

Data from a previous study with 24,217 participants showed that women who underwent a frozen section after a lumpectomy for breast cancer had a four-fold lower risk of needing another surgery. Despite the advantages of macroscopic analysis, the surgeon can do this procedure directly and it yields superior results than other methods in terms of accuracy [80%], sensitivity [49%] and specificity [86%] [10].

FS analysis is the most used intraoperative technique to analyse breast tumour excisions. It involves selecting concerning margins, freezing samples, exposing them to histological sections [usually with a cryostat], and staining them for microscopic examination. However, this raises the possibility of margin injury and a lengthier healing period following surgery [11-13].

High Frequency [HF] ultrasound is another technique to measure the intraoperative margins. Several studies have shown that the propagation of ultrasonic waves in tissues is significantly influenced by histological features such as cell shape, cell density, tissue micro-structure, and tissue heterogeneity [14].

Ultrasound transmission tomography was employed from 2 to 10 MHz and the frequency-dependent attenuation of the ultrasonic wave propagation to classify the tissue in eight mastectomy specimens. The superior spatial resolution of the scans [≤ 1 mm] made a strong correlation with pathological micrographs [15].

The current study was designed as a comparative study to assess the value of FS and IOUS in determination of an appropriate negative margin for conservative breast surgery.

PATIENTS AND METHODS

Thirty females, managed and treated at Al-Hussein and Bab-elshaaria University Hospitals by BCS for early breast cancer [T1-2, N0-1, and M0] were included in this prospective, non-randomized trial.

Ethical consideration: The study protocol had been approved by the local faculty of medicine's ethics committee, and every patient signed an informed consent for participation in the study. Each patient had the right to withdraw at any time without any adverse effects for his treatment plan and the study had been completed in line with the research conduction and reporting guidelines.

The patient was included if she had a solitary mass, with the size < 4 cm, no evidence of multicentricity, and absence of extensive lymph node involvement or diffuse micro-calcification. On the other hand, the exclusion criteria were multicentricity, diffuse malignant mammographic microcalcification, inflammatory carcinoma, scleroderma, pregnancy, central or periareolar tumor, and large tumor in the small breast and in who clear margins can't be assessed without performing a mastectomy.

Patients were divided into two groups, Group-A with intraoperative FS to assess the safety margin, and Group-B with intraoperative ultrasound to assess the safety margin. All patients were assessed for safety margin, patient satisfaction, volume resection, short-term local recurrence, cosmetic result, return to theater, and the operative time.

Preoperative evaluation

Each female was evaluated by full history taking and exhaustive clinical examination [general and local] in a systematic manner [inspection and palpation]. Then, all were staged on a clinical basis. Routine laboratory investigations were carried out to assess the fitness of the patient for surgical intervention. This included complete blood count [CBC], coagulative profile, and tumor markers]. Then a breast mammography was performed.

Surgical procedure

Patients underwent wide local excision including complete tumor removal with the aim of achieving grossly normal tissue margins of at least 1 cm and axillary lymph node clearance. The intraoperative evaluation procedures were based on gross inspection, frozen section, and ultrasound. Then the results were compared to the results of histopathology as the gold standard to estimate the value of each method.

The postoperative follow up included the duration of hospital stay, seroma formation, cosmetic outcome, patient satisfaction, post-surgical complications, and recurrence rate.

Statistical analysis

The statistical package for social sciences [SPSS], version 23.0 [IBM Inc., Chicago, Armonk, USA], was used to analyze the collected data. The numerical variables were presented by their mean, minimum, maximum and standard deviation [SD]. However, the categorical variables were presented by their relative frequency and percentages. The groups were compared by independent sample student "*t*" test, Mann-Whitney "U" when quantitative and by Chi square, Fisher exact test when qualitative. Sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV] and overall accuracy were calculated by appropriate equations after determination of the results to true positive, true negative, false positive and false negative. The one-way analysis of variance [ANOVA] was used to compare between more than two groups. P value < 0.05 was considered significant to interpret the results.

RESULTS

In the current work, the female age ranged between 36 and 72 years. 46.7% of FZ group had no associated comorbid disease compared to 66.7% in group-B. The family history was positive among 13.3% and 26.7% of groups A and B, respectively. Oral contraceptive pills were used by 46.7% and 40.0% of groups A and B respectively. There were no significant differences between groups A and B, regarding the female characteristics [Table 1].

In addition, both groups were comparable regarding tumor characteristics [Details are presented in table 2].

The outcome among study groups showed that FZ was associated with a significant increase of safety margin when compared to IOUS [12.42±2.32 vs 10.22±1.73, respectively]. Both maneuvers showed a significant increase of safety margin when compared to the results of pathology. In addition, there was a significant increase of volume resection and operative time in group A than group B. However, the local recurrence was confined to group A and reported only for one patient with no significant difference between groups [Table 3].

Table [4] presented the value of both methods with histopathology as a gold-standard. FZ sensitivity was 80%, specificity 100%, PPV 100% and NPV 71.4% and accuracy 86.7%. The Kappa agreement 0.727 [0.389-1.00]. In addition, IOUS had sensitivity 100%, specificity 100%, PPV 100% and NPV 100% and accuracy 100%, Kappa agreement 1.00 [1.00-1.00].

Table [1]: Patient characteristics among study groups

Variable	Measures	Group-A [n=15]	Group-B [n=15]	Test	p
Age [years]	Mean ±SD	51.62±9.10	52.33±8.53	0.220	0.827
	Min.-Max.	36-72	36-71		
Associated comorbid conditions [n, %]	None	7 [46.7%]	10 [66.7%]	1.181	0.277
	DM	2 [13.3%]	2 [13.3%]	0.000	1.000
	HTN	4 [26.7%]	2 [13.3%]	0.814	0.367
	ISH	2 [13.3%]	1 [6.7%]	0.351	0.554
Family history [n, %]	Positive	2 [13.3%]	4 [26.7%]	0.208	0.648
	Negative	13 [86.7%]	11 [73.3%]		
Oral contraceptives [n, %]	No	8 [53.3%]	9 [60.0%]	0.133	0.716
	Yes	7 [46.7%]	6 [40.0%]		

Table [2]: Tumor characteristics among study groups

	Tumor characteristics	Group A [n=15]	Group B [n=15]	Test	p
Side	Right	8 [53.3%]	11 [73.3%]	0.574	0.449
	Left	7 [46.7%]	4 [26.7%]		
Tumor site	UOQ	5 [33.3%]	7 [46.7%]	0.542	0.461
	LOQ	4 [26.7%]	3 [20.0%]	0.182	0.670
	UIO	4 [26.7%]	2 [13.3%]	0.367	0.814
	LIQ	2 [13.3%]	3 [20.0%]	0.235	0.628
Pathological type	IDC	12 [80.0%]	10 [66.7%]	0.715	0.699
	ILC	1 [6.7%]	2 [13.3%]		
	Mixed ductal & lobular ca.	2 [13.3%]	3 [20.0%]		
Clinical stage	T1	8 [53.3%]	10 [66.7%]	0.139	0.709
	T2	7 [46.7%]	5 [33.3%]		
Clinical lymph node stage	N0	9 [60.0%]	7 [46.7%]	0.134	0.714
	N1	6 [40.0%]	8 [53.3%]		
Tumor stage	II	9 [60.0%]	11 [73.3%]	1.067	0.302
	III	6 [40.0%]	4 [26.7%]		
Hormone receptor	Luminal A [ER + PR + HER-]	11 [73.3%]	10 [66.7%]	0.150	0.698
	Luminal B [ER + PR + HER+]	2 [13.3%]	2 [13.3%]	0.000	1.000
	Triple negative [ER - PR – HER-]	1 [6.7%]	2 [13.3%]	0.351	0.554
	HER2 positive [ER - PR - HER+]	1 [6.7%]	1 [6.7%]	0.000	1.000

Table [3]: Outcome among study groups

		Group A [n=15]	Group B [n=15]	Pathology	Test	p
Safety margin [mm]	Mean ± SD	12.42±2.32	10.22±1.73	5.29±1.09	4.683	**<0.001***
Volume resection [cm^3]	Mean ± SD	51.14±11.05	42.33±7.29		2.577	**0.016***
Operative time [min]	Mean ± SD	53.86±10.23	40.58±7.71		4.015	**<0.001***
	Min.-Max.	43-65	32-49			
Local recurrence [n, %]	Yes	1 [6.7%]	0 [0.0%]		1.05	0.316
	No	14 [93.3%]	15 [100.0%]			

Table [4]: Comparison between study groups regarding sensitivity and specificity [Histopathology is the gold standard]

	Group A [n=15]	Group B [n=15]
True positive	8	9
True negative	5	6
False positive	0	0
False negative	2	0
Sensitivity%	80%	100%
Specificity%	100%	100%
Positive predictive value	100%	100%
Negative predictive value	71.40%	100%
Accuracy	86.70%	100%
Agreement	0.727	1.000

DISCUSSION

The results of the current work showed that the demographic data did not differ between the study groups, and the majority were in their fifties. Women in both groups were comparable regarding their personal and tumour characteristics. However, frozen section group significantly higher safety margin, resected volume, and longer operative time, when compared to IOUS. One patient reported local recurrence in the FZ group compared to none in IOUS group. Finally, the predictive value of IOUS was better than the FZ.

These results agree with other studies indicating that the likelihood of an ipsilateral breast tumour recurrence is significantly impacted by young age. **Jobsen *et al.*** [16] found that the only significant predictor of ipsilateral breast tumour recurrence among women who underwent breast conserving surgery were pT1 grade malignancies and negative lymph node status in women older than 40 years old. In addition, **Harrold *et al.*** [17] showed a correlation between young age and ipsilateral breast tumour recurrences, using the age of 40 as a cut-off point.

Tenea-Cojan *et al.* [18] conducted a histological analysis of breast carcinomas treated conservatively in 2016. 303 cases of breast carcinomas were analysed by the conventional histological technique of paraffin embedding. They concluded that over half of the cases were carcinomas, measuring between 2 and 5 cm and without associated lymph node involvement, based on the pTNM criteria for stage II. Using univariate statistical analysis, they were unable to find a significant difference between the probability of local recurrence and the kind of breast cancer [invasive, non-invasive, or other; p = 0.6053].

Relapses happened in 79.2% of cases of reported ipsilateral recurrences, mixed ducto-lobular carcinomas in 8.3% of cases, and other kinds of carcinomas in 12.5% of cases, according to a 2011 study by **West *et al.*** [19]. These results also align with the inferences made from our research.

According to **Newman *et al.*** [20], lobular carcinoma's invasive form is likely associated with a higher risk of developing a new primary malignancy of the contralateral breast when compared to other histological types.

Previous studies have reported that the incidence of a significant intraductal component range from 13.3% to 39.0%. Specialized research indicates that a 1999 study by **Freedman *et al.*** [21] only found a considerable intraductal component in 5% of cases. This study included a sample of 1262 patients who underwent conservative breast surgery and had stage I or stage II breast cancer.

Wellings *et al.* [22] state that the term extensive intraductal component has been widely employed to describe an intraductal cancer that has undergone significant growth based on routine histological assessment.

It is important to note that there is no set protocol for assessing the condition of surgical resection margins. **Mansfield *et al.*** [23] assessed this status and gave the same "positive" and "negative" classifications as the current work. **Silverstein *et al.*** [24] evaluated the resection margins based on the distance between the margin and the presence of malignant cells.

Nonetheless, it is significant that this distance ranges from less than 1 mm to less than 10 mm. 24- Despite these limitations, recent studies show that assessing the resection margins' state is still quite useful in predicting the chance of local recurrences.

In their study, **Komoiko *et al.*** [25] showed that young age, positive resection margins, and radiation omission are significant predictors of ipsilateral recurrences.

As in the current work, **Krishnan *et al.*** [26] found a great connection and high accuracy of the ultrasound assessment with the final histological findings. The ultrasound had a 100% sensitivity rate and could accurately predict the margin status 100% of the time. But only in six cases, with an accuracy of 90.32%, there was the worried margin recognized by the frozen section. The ultrasound had a 100% margin assessment sensitivity, whereas the FS had a 62.5% sensitivity. The ultrasound showed that the margins were positive in 16 cases [25.8%] and negative in 46 cases [74.2%]. This exhibited a perfect correlation with histology's results. Out of the 16 cases, ten [16.13%] also had favourable results on the FS. The margins were re-executed on the table in each of the sixteen instances, and new margins were tagged and sent in for final histopathology. The histological assessment confirmed the presence of disease [invasive or in-situ] in the margins that were sent out separately in each of these sixteen cases. The accuracy of the ultrasound assessment was strongly correlated with the final histological findings. The ultrasound had a 100% sensitivity rate and could accurately predict the margin status 100% of the time. But only in six cases—with an accuracy of 90.32%—was the worried margin recognized by the FS. The ultrasound had a 100% margin assessment sensitivity, whereas the frozen part had a 62.5% sensitivity.

Conclusion: In conservative breast surgery, intraoperative ultrasonography provides more precise results for determining safety margins than frozen section. However, results must be treated cautiously due to the small numbers of included subjects, which represent a limiting step of the current work. Future large-scale studies are recommended.

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