Margin Assessment in Breast Conservative Surgery and Concordance between Frozen and Paraffin Section Results: A Retrospective Study

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Abstract

Background: Breast-conserving therapy (BCT) is an alternative to mastectomy for treatment of breast carcinoma. Negative surgical margins minimize the risk of local recurrence after breast-conserving surgery. Intraoperative frozen section analysis (FSA) is one method for margin evaluation.

Aim of Study: The study aimed to determine the concordance between results of frozen section examination (FSE) and the final paraffin section in assessing margin status in breast conservative surgery and to study re-excision rates and local control of disease in patients subjected to FSE.

Patients and Methods: This was a retrospective cohort study, was carried out on 30 women with early breast cancer undergoing breast conservative surgery, at General Surgery Department, Ain Shams University Hospitals, from June 2021 to June 2022. All patients were subjected to Detailed history taking, clinical examination, lab Investigations and Frozen section analysis.

Results: The mean age of the study population was 48.53 ± 7.82 years and 63.3% of them were older than 50 years with mean BMI was 25.75kg/m² and (56.7%) of them were rural. Regarding adjuvant therapy, 13.3% of the patients underwent chemotherapy, 56.7% of the patients underwent endocrine therapy and 10% underwent both therapies. 30% of the patients had positive margins and underwent additional resections. Out of 21 negative margins by FSA there were 2 of them were positive in final section with false negative of 5%. FSA was significant in assessing margin status with sensitivity of 80%, specificity 95%, NPV 94.5%, PPV 88.9% and accuracy of 90%.

Conclusion: There is good concordance between results of FSA and the final paraffin section in assessing margin status. Frozen section diagnosis is an accurate method for the assessment of surgical margin clearance.

Key Words: Margin assessment – Breast conservative surgery – Concordance – Frozen – Paraffin section.

Introduction

WORLDWIDE, breast cancer is the most common cancer in women, other than non-melanoma skin cancer [1].

Due to the screening programs, breast cancer is detected at earlier stages, with the detection of non-palpable lesions and in situ carcinomas increasing in up to approximately 20% of the newly diagnosed primary cases [2].

By detecting breast cancer at an earlier stage and by developing better treatment approaches, survival rates are improving and the illness is mostly curable. For most patients with early breast cancer, surgical intervention serves as the first phase of treatment [3].

Breast conserving therapy (BCT) is the preferred treatment approach for most patients with early-stage breast cancer (T1, N1, M0, according to TNM staging). The combination of complete resection of the primary lesion with tumor-free margins and radiotherapy provides excellent local tumor control [4].

Breast cancer is a histologic diagnosis made according to standardized pathologic criteria. The most common breast cancer histology is invasive ductal carcinoma (50%-75% of patients), followed by invasive lobular carcinoma (5%-15% of patients), mixed ductal/lobular carcinomas and other rarer histologies making up the remainder of patients [5].

Because pathologic margin status is an important prognostic factor for local recurrence after segmental resection of in situ or invasive breast carcinoma, pathologic examination of margin status plays a key role in BCT. The inability to obtain clear margins at the time of partial mastectomy for malignancy remains a significant clinical problem [6].

One of the tools that can be used to evaluate the adequacy of the BCT procedure is the intraoperative pathologic analysis of a tissue sample, to
evaluate surgical margins \[?\]. The most common technique used for this purpose is a microscopic frozen-section analysis (FS). However, when compared to the final pathologic analysis of paraffin blocks, this method shows some limitations. First of all, it is characterized by considerably lower sensitivity of 65-78\%, and its use extends the surgical procedure duration \[8\].

Other diagnostic methods can also be used for the intraoperative assessment of surgical margins, including: Radiological studies (mammography - MMG, ultrasound scan - USS), fluorescent techniques (using indocyanine green and IR Dye 800CW), optical techniques (based on the light spectrum analysis), isotopic methods (using 111In or 89Zr) and other pathologic techniques: Touch imprint cytology, macroscopic and microscopic margin assessment \[9,10\].

All methods used for intraoperative evaluation of margin status have some technical or practical limitations. For example, segmental resection specimens have a large surface area and are often irregular, making it difficult for the pathologist and surgeon to determine the “true” margin, even if orientation and inking methods are used. Any technique used to evaluate margin status in the operating room must be relatively simple, rapid, reproducible, and inexpensive for it to be practical and cost-effective \[11\].

The status of the surgical margins is assessed by applying ink to the surface of the lumpectomy specimen and determining the microscopic distance between tumor cells and the inked surface \[12,13\].

**Aim of the work:**

The study aimed to determine the concordance between results of frozen section examination (FSE) and the final paraffin section in assessing margin status in breast conservative surgery and to study re-excision rates and local control of disease in patients subjected to FSE.

**Patients and Methods**

This was a retrospective cohort study, was carried out on 30 women with early breast cancer undergoing breast conservative surgery; at General Surgery Department, Ain Shams University Hospitals, from June 2021 to June 2022. Women with breast cancer undergoing breast conservative surgery.

**Inclusion criteria:**

Women with a pre-operative fine-needle aspiration cytology or tru-cut biopsy diagnosis of in situ or invasive carcinoma with or without neoadjuvant treatment, those patients underwent breast conservative surgery with intraoperative frozen section examination for margin status. We would choose: Patients with invasive ductal carcinoma (NOS), early breast cancer up to T2N1M0.

**Exclusion criteria:**

Bilateral breast cancer, diffuse micro calcifications, patients with multifocal and multicentric tumor which is an indication for modified radical mastectomy.

Explanation of the procedure to all women participating in the study was done. A written consent was taken from all patients before the operation. Sampling method: The last 30 patients in the surgical database fitting to inclusion and exclusion criteria.

**Methods:**

**Detailed history taking including:**

Personal history: Age, sex, occupation and marital state, patients' socioeconomic status would be assessed using the socioeconomic scale (SES), history of chronic diseases including the hypertension, diabetes mellitus and cardiac diseases, history of obesity, drug intake or smoking, history of the current illness: Onset, course and duration of any complain as breast pain, nipple discharge, and mass, family history of breast cancer, review of all previous investigations or radiological examination, past history (previous operations, chronic medical diseases, drugs).

**Careful clinical examination:**

A- General: Blood pressure, pulse, cardiovascular, neurological and respiration assessment, weight measurement

B- Investigations: Mammography - MMG, ultrasound scan - USS, liver function tests (AST, ALT, ALP, serum bilirubin, serum albumin, Prothrombin time and I.N.R.), serum creatinine, complete blood count (CBC), HBsAg, HCV Ab, HBA1C for diabetic patients, lipid profile.

**Main outcome measures:**

The incidence of having infiltrated positive margin in paraffin section sample despite having negative margins by frozen section examination technique.

**Statistical analysis:**

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows (SPSS
Inc., Chicago, IL, USA) & MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi^2$) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation). Sensitivity, specificity, positive and negative predictive value as well as accuracy are expressed as percentages.

Results

Table (1): Demographic distribution of the studied patients.

<table>
<thead>
<tr>
<th>All patients (n=30)</th>
<th>Age (years) Mean ± SD</th>
<th>&lt;50 years 19 (63.3%)</th>
<th>&gt;50 years 11 (36.7%)</th>
<th>BMI (kg/m$^2$) Mean ± SD</th>
<th>Rural 17 (56.7%)</th>
<th>Urban 13 (43.3%)</th>
</tr>
</thead>
</table>

This table shows that mean age of the study population was 48.53 ± 7.82 years and 63.3% of them were older than 50 years with mean BMI was 25.75 kg/m$^2$ and (56.7%) of them were rural.

Table (2): Pathologic tumor size among the studied patients.

| All patients (n=30) | Pathological tumor size (cm) Mean ± SD | Tis 4 13.3 | T1 18 60 | T2 8 26.7 |

This table shows that 13.3% of the patients were Tis, 60% of the patients were T1 and 26.7% of the patients were T2 with mean size was 2.73 ±0.964 cm.

Table (3): Radiological findings distribution among the studied patients.

<table>
<thead>
<tr>
<th>All patients (n=30)</th>
<th>Palpable:</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non- Palpable breast tumor</td>
<td>5</td>
<td>16.7</td>
<td></td>
</tr>
<tr>
<td>Palpable breast tumor</td>
<td>25</td>
<td>83.3</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

Accurate intra-operative assessment of margin status can overcome such problems to a large extent. Intra-operative frozen section is a suitable technique for intra-operative assessment of margins [14].

The use of intraoperative evaluation and frozen section of surgical margins is a common and practical procedure used in cancer resection of much organ system [15].

In previous studies, the authors have accepted that tumor recurrence rate is extremely higher in patients who have tumor cells on the surgical margin of the specimen. Radiotherapy alone cannot compensate for inadequate surgery [16].

The study aimed to determine the concordance between results of frozen section examination (FSE) and the final paraffin section in assessing
Margin status in breast conservative surgery which would affect re-excision rates and local control of disease in patients subjected to FSE.

This was a retrospective cohort study, was carried out on 30 women with early breast cancer undergoing breast conservative surgery; at General Surgery Department, Ain Shams University Hospitals, from June 2021 to June 2022.

Analysis of our findings revealed that the mean age of the study population was 48.53 ± 7.82 years and 63.3% of them were older than 50 years with mean BMI was 25.75 kg/m² and (56.7%) of them were rural.

This comes in comparison with the study of Anila et al. [17] which was carried out on a total of 60 patients with the median age at diagnosis was 46 years (range 23-71 years); 35% of them were older than 50 years.

Another study of Farouk et al. [18] which was evaluated 219 patients with breast cancer with mean ± SD age 48 ± 10 ranging from 23-76 years.

Furthermore, the study of Liu et al. [19] was conducted on a total of 1,340 breast cancer patients included in their study. Most BCS patients were 40-60 years old, lived in urban areas, were of the Han nationality, had medical insurance, had higher personal income, and were well educated.

In the current study, we found that about 13.3% of the patients were Tis, 60% of the patients were T1 and 26.7% of the patients were T2 with mean size was 2.73 ± 0.964.

While in the study of Da Silva et al. [20] in which mean age was 50.5 years (standard deviation, SD 10.7). Furthermore, most women were non-Caucasian (53.8%). At diagnosis, most patients had outer quadrant (57.9%) and advanced clinical stage tumors (stage III: 83.6%; cT3/T4: 85.9%; cN1-3: 71.3%). In addition, the predominant histological subtype was high-grade (67.3%) and invasive ductal carcinoma (93.6%).

In another study done by Sezgün et al. [22] reported that the mean age was 53.8 ± 13.4 years (median 51, range 31-90). The mean pathologically determined tumor size was 30.3 ± 22.2 mm (median 25mm, range 7-150mm); the tumor size was determined to be 29.4 ± 21.1 mm (median 24mm, range 6-138mm) with MRI, 20.1 ± 8 mm (median 20mm, range 5-141mm) with MM, and 20.1 ± 11.4 mm (median 18mm, range 5-66mm) with US. Thirty-two patients (35.2%) had multifocal or multicentric breast cancers.

In the study on our hands, about 16.7% of the patients had non-palpable breast tumor and 83.3% of the patients had palpable breast tumor in radiology.

In agreement with our findings, the study of Anila et al. [17] reported that the mean pathological tumor size was 3.02 cm (range 1-4.5 cm). The majority of patients 55 cases (92%) presented with palpable breast tumors and these cases had a core biopsy or fine needle aspiration based pathologic diagnosis prior to BCS. Five patients had radiologically detected non-palpable tumors.

In a harmony with the study of Anila et al. [17] reported that Twenty-nine patients (48.33%) had pathologically node positive disease of which 18 patients had 1-3 positive nodes and 11 patients had four or more positive nodes.

However, Li et al. [23] reported that about 60 percent of the women in their study were 50 years of age or older. Women with small tumors (≤ 2.0 cm in diameter) and women with large tumors (2.1 to 4.0 cm in diameter) were uniformly distributed among the treatment groups. Slightly more than 50 percent of the women had small tumors, and slightly less than 50 percent had large tumors.

Frozen-section analysis (FSA) is one of the most useful methods [24].

The cornerstone finding of our study was that about 30% of the patients had positive margins and underwent additional resections.

In a study of Tamanuki et al. [25] reported that 21 patients (15%), frozen section analyses (FSA) revealed positive margins, resulting in immediate re-excision. In seven of these patients (5%), margins were persistently positive, and these patients therefore underwent mastectomy. Fourteen patients were successfully re-excised to a negative margin. The sensitivity and specificity of FSA were 91% and 100%, respectively. Five percent of patients definitively managed by lumpectomy with FSA of margins recurred locally.

Furthermore, in the studied patients, out of 21 negative margins by FSA there were 2 of them were positive in final section with false negative of 5%.

Tamanuki et al. [25] reported that among 386 patients not subjected to frozen section for intraoperative margin assessment because of an imprint cytology-negative diagnosis, 11 (2.1%) were permanent sections-positive, i.e., imprint cytology-
false-negative. In 47 (34.6%) of 136 imprint cytology-positive patients, additional intraoperative excision was unnecessary due to the frozen section-negative diagnosis. Therefore, 11 patients (2.1%) underwent unnecessary excision (false-positive rate of imprint cytology+frozen section, 19%) and after undergoing excision, 4 still had positive margins (permanent sections-positive). The overall positive margin rate in the final pathology based on permanent sections was 2.9% (15/522).

Cendan et al. [26] reported that forty-three patients had positive margins on paraffin-embedded histologic analysis (44.3%). Accuracy of FSA was 84% when evaluated on a per-case basis, and 96% on a per-slide basis. False negatives were identified in 22 patients, affecting the operative pathway of 19 patients (19.6%) and were identified more frequently in cases of ductal carcinoma in situ (p < 0.001). There were no false positives.

Finally, in our study, we found that FSA was significant in assessing margin status with sensitivity of 80%, specificity 95%, NPV 94.5%, PPV 88.9% and accuracy of 90%.

In a metaanalysis of Garcia et al. [14] Sensitivity and specificity were evaluated in 17 studies; Intra-operative assessment sensitivity was 0.81, with a CI of 0.79-0.83, p = 0.0000, and inconsistency (I²) of 95.1%, which included the analysis of 5,615 tests in total. Specificity was 0.97, with a CI of 0.97-0.98, p = 0.0000, and inconsistency of 90.8% in the same sample. The accuracy, represented by the area under the SROC curve, is near to 1.0.

Tamhane et al. [27] reported that the sensitivity, specificity, PPV, NPV, and accuracy of frozen section diagnosis for surgical margins were found to be 100%, 98.71%, 100%, 97.08%, and 99.02%, respectively. The correlation between frozen section diagnosis and histopathological diagnosis was significant with “p” value of 0.0001. The correlation between TIC and that of histopathological diagnosis also was found to be significant which 0.001 was. The sensitivity, specificity, PPV, NPV, and accuracy of TIC for surgical margins were found to be 46.51%, 90.76%, 56.56%, 84.62%, and 86.40%, respectively.

Schulz-Wendtland et al. [29] performed a retrospective analysis of frozen section margin accuracy compared to permanent sections and showed an 84% concordance, with 24% of the patients requiring immediate re-excision intraoperative of the lesion and approximately 20% of patients needing second surgery due to false-negative margins. The findings of the present study showed an accuracy rate of 100% in cases of carcinoma of the breast for surgical margins.

Chakravorty et al. [30] studied 146 patients in 2012 with positive resection margins in 2.7% cases, with a local recurrence of 4.3% cases in carcinoma of the breast patients. In the present study, there were no positive resection margins on frozen sections as well as histopathology.

In a meta-analytical study carried out by Esbona et al. [31] the authors studied five TIC studies and nine frozen section diagnosis studies to analyze pooled intraoperative sensitivity and specificity. The sensitivity of frozen sections (83 ± 13%) versus TIC (72 ± 38%) was not significantly different (p = 0.53). Similarly, the specificity of frozen sections (95 ± 8%) versus TIC (97 ± 3%) was not significantly different (p = 0.58). In the present study, the sensitivity and specificity of frozen section diagnosis and TIC were found to be 100%, respectively, for carcinoma of the breast.

Conclusion:
Intra-operative FSA allows resection of suspicious margins at the time of primary conservative surgery and results in low rates of local recurrence and second surgeries. There is good concordance between results of FSA and the final paraffin section in assessing margin status. Frozen section diagnosis is an accurate method for the assessment of surgical margin clearance.

References


