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Cancer

Diabetes

Cardiovascular Diseases

Chronic Respiratory Diseases

The Official Journal of the Gulf Federation For Cancer Control
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Introduction: Intraoperative frozen section of sentinel lymph nodes (SLN) in clinically node-negative breast cancer patients is performed to stage the axilla and allows axillary lymph node dissection (ALND) to be avoided in the same operative setting. The aim of this study was to evaluate our institutional experience on the accuracy of intraoperative frozen section of sentinel lymph node biopsy (SLNB) in breast cancer patients.

Methods: Clinicopathological data from patients who underwent surgery for breast cancer with SLNB from January 2013 to May 2017 at Salmaniya Medical Complex (SMC) in Bahrain were collected retrospectively. Results of intraoperative frozen section were compared to paraffin section to determine accuracy, sensitivity, specificity, positive—predictive value (PPV), negative—predictive value (NPV) and false—negative rate (FNR).

Results: A total of 104 patients with breast cancer underwent breast surgery with SLNB and intraoperative frozen section evaluation of SLNB. Frozen section correctly identified a positive or negative result in 97 cases (accuracy 93.2%). The sensitivity was 77.7%. The specificity was 98.7%. The PPV was 95.4%. The NPV was 92.6%. The overall FNR was 22.3%.

Conclusion: Our results show that intraoperative frozen section can reliably evaluate the status of SLNB in patients with breast cancer, allowing us to avoid second stage surgery in most women.

Keywords: breast cancer, frozen section, sentinel lymph node biopsy, axillary lymph node dissection.

Introduction

Axillary lymph node status is regarded as one of the most important prognostic indicators in breast cancer, particularly for the selection of adjuvant therapy. In the past, conventional ALND was routinely performed to stage the axilla and treat axillary disease, but this is associated with higher incidence of complications, such as seroma, wound infection, lymphoedema, paraesthesias and limited shoulder movements. SLNB is now established as the standard of care to evaluate axillary lymph node status in early—stage, clinically node—negative breast cancer, avoiding unnecessary ALND. Compared to ALND, patients who undergo SLNB have less postoperative morbidity in terms of associated surgical complications. ALND remains the standard of treatment when a positive SLN is found, but this has become controversial with the publication of the ACOSOG Z0011 study, which concluded that routine use of ALND is not justified in certain patients despite having a positive SLN.

Since the introduction of SLNB in the management of breast cancer, methods for rapid assessment of SLN included frozen section and imprint cytology. Although the gold standard is examining a paraffin—embedded section, intraoperative frozen section at the time of SLNB allows ALND to be avoided if negative. There is a growing evidence in the literature regarding reliability of intraoperative frozen section during SLNB. At our institution, SLNB with frozen section was introduced in 2010 by a multidisciplinary team to allow accurate staging of axillary lymph node status and to avoid unnecessary ALND. SMC is the main hospital in Bahrain where this technique is routinely performed for management of early—stage, clinically node—negative breast cancer. The aim of this study was to present our experience of SLNB with intraoperative frozen section assessment in women with breast cancer and contribute to the literature regarding its reliability and utility in the staging of axillary lymph node status.
Methods

Patients

Between January 2013 and May 2017, a total of 122 women underwent surgery for breast cancer, either partial or total mastectomy with SLNB and intraoperative frozen section assessment by one of the two general surgical oncologists (RA or AA) at SMC. 104 patients with clinically node-negative, operable breast cancer were eligible for inclusion in the study and were retrospectively analyzed. The exclusion criteria included: patients post-neoadjuvant chemotherapy (NAC), cases where frozen section was not done due to technical limitations or failure to localize SLN. All patients were consented for the planned procedure and were well informed about the possible need for immediate ALND (if the SLN was found to be positive for cancer cells by frozen section) or staged ALND (if SLN was negative by frozen section but positive by permanent section).

Surgical technique

Our method of detection of SLN involves the use of both radioactive colloid and blue dye. Radioisotope tracer (99m-Tc–labelled colloid) was injected into the periareolar region few hours preoperatively on the day of surgery. After induction of general anesthesia, blue dye was injected intraparenchymally into the periareolar region. The SLN was detected intra-operatively by visual inspection for blue dye as well as hand-held gamma-probe guidance. All SLN identified were sent for frozen section. While the lymph nodes were analyzed by frozen section, the primary tumor was resected and sent for histopathological examination. Patients found to have more than two positive SLN (in those undergoing partial mastectomy) or single positive SLN (in those undergoing total mastectomy) underwent immediate ALND. In patients with two or less positive SLN (in those undergoing partial mastectomy and where postoperative adjuvant radiotherapy was planned), no further ALND was done in keeping with ACOSOG Z0011 recommendation.

Histopathological technique

Consultant pathologists examined the lymph nodes both by imprint cytology and frozen section. Each lymph node was bisected and serially sliced perpendicular to its long axis. The specimen was imprinted onto a slide, which was then stained with modified Giemsa stain (Diff Quick). The entire lymph node was submitted for frozen section, which was prepared using hematoxylin and eosin (H&E) and examined microscopically. Both the imprint cytology and frozen section results were communicated to the operating surgeon within 30–45 minutes. The remaining tissue specimen was fixed in formalin and embedded in paraffin. The pathologist examined this permanent section, stained with H&E, postoperatively.

Data collection and analysis

For all patients: age, gender, tumor laterality, tumor location, tumor size (T stage), histological tumor type, tumor grade, number of retrieved SLN, frozen section result, subsequent final histopathology result, lymph node status after ALND and type of surgery were collected and recorded in a database.

Data analysis

The results of intraoperative frozen section SLNB were compared with final histopathological examination to calculate accuracy, sensitivity, specificity, PPV, NPV and

<table>
<thead>
<tr>
<th>Age</th>
<th>51</th>
</tr>
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<tbody>
<tr>
<td>Median</td>
<td>50</td>
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<tr>
<td>Range</td>
<td>29-76</td>
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<table>
<thead>
<tr>
<th>Laterality</th>
<th>Right breast</th>
<th>58 (55.7%)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Left breast</td>
<td>46 (44.3%)</td>
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<table>
<thead>
<tr>
<th>Tumor location</th>
<th>One quadrant</th>
<th>57 (54.8%)</th>
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<tbody>
<tr>
<td></td>
<td>Multicentric</td>
<td>8 (7.69%)</td>
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<tr>
<td></td>
<td>Unknown</td>
<td>38 (37.5%)</td>
</tr>
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<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Partial mastectomy</th>
<th>60 (57.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total mastectomy</td>
<td>44 (42.4%)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>T1</th>
<th>4 (3.84%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T2</td>
<td>40 (38.4%)</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>5 (4.80%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>DCIS</th>
<th>4 (3.84%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>IDC (non-specific)</td>
<td>89 (85.5%)</td>
</tr>
<tr>
<td></td>
<td>ILC</td>
<td>6 (5.76%)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Medullary carcinoma</th>
<th>2 (1.92%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mucinous carcinoma</td>
<td>1 (0.96%)</td>
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<tr>
<td></td>
<td>Tubuloloobular carcinoma</td>
<td>1 (0.96%)</td>
</tr>
<tr>
<td></td>
<td>Cribriform carcinoma</td>
<td>1 (0.96%)</td>
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</table>

<table>
<thead>
<tr>
<th>Tumor grade</th>
<th>Grade I</th>
<th>12 (11.5%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Grade II</td>
<td>50 (48.0%)</td>
</tr>
<tr>
<td></td>
<td>Grade III</td>
<td>38 (36.5%)</td>
</tr>
<tr>
<td></td>
<td>Not applicable (DCIS)</td>
<td>4 (3.84%)</td>
</tr>
</tbody>
</table>

Table 1. Patient and tumor characteristics
FNR and statistical analysis was done using the SPSS software.

Results

Patient and tumor characteristics

The clinicopathological characteristics of our study population are summarized below (Table 1). A total of 104 patients who underwent surgery for breast cancer and SLNB with intraoperative frozen section were included in the study. Their mean age was 51 (median 50, range 29–76). 58 cancers were left–sided and 46 were right–sided. 57 cases were limited to one breast quadrant and 8 were multicentric, but tumor location was unknown in 38 cases. 60 patients underwent partial mastectomy (seven required wire–guided localization), while 44 patients underwent total mastectomy due to one of the following: high tumor:breast volume ratio, central location, multicentric tumor or patient preference. On final histopathology report, four patients were found to have Tis tumors, while 55 were T1, 40 were T2 and five were T3. 89 cases were non–specific invasive ductal carcinoma (IDC) in type, five were specific IDC subtypes, six were invasive lobular carcinoma (ILC) and four were ductal carcinoma in–situ (DCIS). On Bloom Richardson grading system, 12 were Grade I, 50 were Grade II, 38 were Grade III and in four cases the grade was not applicable (DCIS).

Frozen section and final histopathology

The mean number of SLN excised was 2. Frozen section correctly identified nodal metastases in 21 patients. All patients who had a positive frozen section result and, in keeping with the study surgical technique and protocol underwent immediate ALND, except for one patient, who had staged ALND due to time constraints. There was one false–positive result, due to atypical cells identified at the time of frozen section that could not be confirmed by the histopathologist. 82 patients had a negative frozen section result, but six of these were found to have metastases (five with macrometastases and one with micrometastases) on final histopathology. All patients with axillary nodal macrometastases on final histopathology underwent ALND at a second operation.

Axillary lymph node dissection

21 patients underwent immediate ALND, whereas five patients had staged ALND. Two patients with false–negative frozen section results did not have ALND, one due to micrometastasis and the other because of only one positive SLN in a patient who underwent partial mastectomy. The mean number of lymph nodes harvested at ALND was 19 (range 7–40). 18 patients had further axillary lymph node metastasis found in the ALND specimen (mean 8 nodes). In five cases that had immediate ALND and four patients that had staged ALND, no further nodal metastases was identified at axillary dissection indicating that the SLNs sent for frozen section were the only positive lymph nodes.

Comparison of frozen section with final histopathology

Data regarding accuracy, sensitivity and specificity as well as PPV, NPV and FNR by tumor size and grade is shown below (Table 2 and Table 3). Overall, frozen section correctly identified the presence of tumor cells

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Final histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>Positive</td>
</tr>
<tr>
<td>Frozen section</td>
<td>Positive: 21</td>
</tr>
<tr>
<td></td>
<td>Negative: 6</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>77.7%</td>
</tr>
<tr>
<td>Specificity</td>
<td>98.7%</td>
</tr>
<tr>
<td>PPV</td>
<td>95.4%</td>
</tr>
<tr>
<td>NPV</td>
<td>92.6%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>93.2%</td>
</tr>
<tr>
<td>FNR</td>
<td>22.3%</td>
</tr>
</tbody>
</table>

Table 2. Overall relationship between frozen section and final histopathology (significance level P<0.0001)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>72.7%</td>
<td>85.7%</td>
<td>50%</td>
<td>66.7%</td>
<td>70%</td>
<td>84.6%</td>
</tr>
<tr>
<td>Specificity</td>
<td>97.7%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>97.3%</td>
<td>100%</td>
</tr>
<tr>
<td>PPV</td>
<td>88.8%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>87.5%</td>
<td>100%</td>
</tr>
<tr>
<td>NPV</td>
<td>55.4%</td>
<td>92.8%</td>
<td>75%</td>
<td>50%</td>
<td>92.5%</td>
<td>92.5%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>92.7%</td>
<td>95%</td>
<td>80%</td>
<td>91.6%</td>
<td>92%</td>
<td>94.7%</td>
</tr>
<tr>
<td>FNR</td>
<td>27.3%</td>
<td>14.3%</td>
<td>50%</td>
<td>31.3%</td>
<td>30%</td>
<td>15.4%</td>
</tr>
</tbody>
</table>

Table 3. Relationship between frozen section and final histopathology by T stage and tumor grade

Figure 1. Relationship between frozen section and histopathology by T stage
in 97 cases, so the accuracy was 93.2%. The sensitivity was 77.7%. The specificity was 98.7%. The PPV was 95.4%. The NPV was 92.6%. The FNR was 22.3%. These results proved to be statistically significant (P<0.0001).

The importance of tumor size and grade as indicators of axillary nodal metastases by frozen section was analyzed. The accuracy of frozen section was somewhat higher in T2 than T1 tumors (95% vs. 92.7%, respectively), but lower in T3 tumors (80%), probably due to small sample size (Figure 1). Patients with Grade III tumors had higher accuracy rates than Grade I and Grade II cases (94.7% vs. 91.6% vs. 92%, respectively; Figure 2). On formal statistical analysis, no significant difference was demonstrable between these groups.

Discussion and Conclusion

Role of frozen section

Intraoperative assessment of SLN by frozen section avoids ALND if negative for metastasis and allow for immediate ALND if positive, thus avoiding a second staged operation. Despite a sensitivity of 77.7% (literature range 48–100%), the value of frozen section in this study lies in its specificity (98.7%). Due to the large number of cases with true–negative results (Figure 3), the predictive value of a negative frozen section result was reasonably high at 92.6%. This means that more than 90% of patients will avoid ALND. Among the pitfalls of frozen section are the possibility of false–negative and false–positive results, 5.76% and 0.96%, respectively, which are dependent upon patient demographics and the incidence of axillary nodal metastases in each hospital. 13 Other drawbacks include increased cost, operating time, need for experienced surgeons and pathologists and greater risk of patient anxiety associated with the need for a staged ALND if a false–negative result is found. As well, there is a risk of exposing women without nodal disease to unnecessary ALND if a false–positive result is found. While imprint cytology has been suggested as another method for intraoperative assessment of SLN, emerging evidence in the literature shows that frozen section is comparable, or even superior, to imprint cytology, but when both techniques are combined, diagnostic accuracy is increased.17

Role of ALND

Patients with positive SLN should have ALND in order to stage the disease and give further prognostic information as the proportion of lymph nodes involved can influence patient outcomes.18 However, evidence from the ACOSOG Z0011 randomized controlled trial11 suggested that, in patients with limited axillary nodal metastatic disease (<2 positive SLN) treated with partial mastectomy and planned for adjuvant radiotherapy, there is no benefit from ALND in terms of disease–free survival. In the AMAROS study,19 adjuvant radiotherapy after positive SLNB was found to provide an excellent alternative to ALND for patients with T1–2 breast cancers with less morbidity. Based on these trials, some centers advocate radiotherapy to the axilla for positive nodes rather than doing ALND, but further evidence is required to justify this approach.

Our experience

In this study, the use of intraoperative frozen section of SLNB allowed 97 (93.2%) patients to have their axilla correctly staged in a single procedure. A reoperation rate of 4.80% seems justifiable in the light of 76 patients with true–negative frozen section result who avoided unnecessary surgical morbidity of ALND. After comparing the frozen and final histopathology results, we evaluated reasons for discrepancy. The six false–negative cases were attributed to micrometastases, reactive cells, and suspicious cells, which could not be confirmed by the pathologist intraoperatively. Our FNR was 22.3% (or 19.2% on exclusion of one case due to micrometastasis) and this is acceptable when compared to the literature,
where a systematic review²⁰ of 69 trials of SLNB identified a FNR of 7.3% (range 0 to 29%), with many concluding that a false-negative result is mainly due to failure of frozen section to detect micrometastases and isolated tumor cells. This variation in FNRs is attributed to many factors, including sample size, patient characteristics, hospital protocol and axillary nodal involvement. We had one patient with a false-positive result, who underwent immediate ALND, which would not otherwise be performed. In this case, the final histopathology reported reactive sinus histiocytosis, which created the source of confusion to the pathologist. In one study, indeterminate cases due to reactive histiocytosis were found difficult to distinguish from a micrometastasis.

Role of SLNB after NAC

NAC is used in locally advanced breast cancer cases to downsize the tumor, allowing breast-conserving surgery rather than total mastectomy. In this study, we excluded patients who underwent NAC because the utility of SLNB in these patients has not been well established. The risk of high FNR is a major concern in implementing SLNB in patients after NAC. Based on current evidence, initially node-negative patients prior to NAC who remain node-negative after NAC should undergo post-NAC SLNB, while node-positive patients prior to NAC who become clinically node-negative after NAC should undergo axillary ultrasound to guide axillary surgery. Patients who remain clinically node-negative after NAC should undergo ALND. However, two trials found that targeted axillary dissection, a procedure that involves percutaneous clip placement in the axillary lymph node at diagnosis of node-positive disease with removal of the clipped node during SLNB after NAC, may help to decrease the FNR of SLNB in these patients.

Conclusion

In conclusion, our experience in Bahrain determines that SLNB with intraoperative frozen section is a reliable and minimally invasive technique for staging the axilla in a single-stage operation, preventing unnecessary ALND. We propose that a similar study is required with special emphasis on the accuracy and role of SLNB with intraoperative frozen section in patients who underwent NAC.

Ethical Statement

The study method was reviewed and approved by the local hospital ethics committee.

References


