Malaysian J Pathol 2018; 40(2) : 121 – 128

ORIGINAL ARTICLE

Intraoperative frozen section sentinel lymph node assessment in breast cancer: A tertiary institution experience

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Abstract

Introduction: Intraoperative frozen section lymph node assessment helps to predict axillary lymph node metastasis in breast cancer. However, the accuracy of this frozen section analysis may vary among institutions. This study describes our institution's experience in intraoperative analysis of sentinel lymph node and aims to determine the accuracy, sensitivity and specificity of our assessment. *Materials and Methods:* We retrospectively analysed the histopathological material and data from 82 breast cancer patients diagnosed over a period of four years who underwent intraoperative frozen section evaluation of sentinel lymph nodes. *Results:* Frozen section analysis detected metastasis in 13 out of 82 cases and definitive pathological examination on the paraffin section confirmed these positive findings. There was no false positive case (specificity of 100%). The true positive cases comprised seven macrometastases, five micrometastases and one isolated tumour cells. Sampling error was noted in two cases in which the malignant cells were only present in the deeper final paraffin sections (false negative rate of 13.3%). The test sensitivity was 86.7% and the accuracy rate was 97.5%. These findings are comparable to other published data. *Conclusion:* Intraoperative frozen section analysis is a safe and reliable method for assessment of sentinel lymph node. Knowledge on limitation of frozen section analysis with diligent evaluation of frozen section specimen will be beneficial in reducing interpretation error.

Keywords: Axillary lymph node, breast cancer, frozen section, intraoperative consultation, sentinel lymph node

INTRODUCTION

Breast cancer is the most common cancer in Malaysia accounting for 16.5% of all malignancies followed by colorectal and lung cancer.[1] Sentinel lymph node is defined as the first lymph node that receives lymphatic drainage from the malignant tumour area. Intraoperative lymphatic mapping accurately identifies the sentinel lymph nodes which can be submitted as frozen section for assessment of metastasis.[2]

The frozen section was popularised by Mayo Clinic in 1905 and the technique was published in the same year.[3] Since then, frozen section has been used for assessment of various histological specimen including sentinel lymph node in breast cancer.

Intraoperative sentinel lymph node assessment is commonly performed in breast cancer, including ductal carcinoma in-situ, to assess for possible nodal metastasis. It accurately stages the lymph node without the morbidity of axillary lymph node dissection. Cases of ductal carcinoma-in-situ (DCIS) also warrant intraoperative sentinel lymph node assessment as it has been shown that micrometastasis or macrometastasis may occur in approximately 1.3% of these patients.[4] We are now seeing an increasing trend in intraoperative sentinel lymph node assessment for DCIS with up to 65.1% of DCIS cases are subjected to this analysis.[5]

Macroscopic intraoperative assessment of sentinel lymph node is not accurate and shows poor sensitivity and specificity in detecting metastasis.[6] Currently, intraoperative frozen sections and final paraffin sections analysis of sentinel lymph node are the gold standard

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to identify nodal metastasis accurately. Other methods including intranodal pressure, imprint cytology, intraoperative immunohistochemistry study and one-step nuclei acid amplification (OSNA) assays for cytokeratin 19 mRNA, have also been utilised in nodal metastasis identification.[7,8]

Positive intraoperative sentinel lymph node predicts the likelihood of non-sentinel lymph node metastasis. The correct diagnosis of positive intraoperative sentinel lymph node is important and guides the decision to perform immediate axillary lymph nodes dissection in the same operative setting. This effectively reduces the number of patients going for second operation.[9,10] Sentinel lymph node dissection is a safe technique and has been proven in multiple studies to have lower incidence of complication compared to axillary lymph nodes dissections. Despite that, the risk is not negligible as some of these patients develop long term arm and shoulder morbidity following surgery.[11]

Although assessment of sentinel lymph nodes in breast cancer center is being carried out in some institution in Malaysia, there has been few studies to evaluate its performance.[12] In the current report, we evaluated the results of our institution's intraoperative frozen section axillary sentinel lymph node assessment and correlated it to the final paraffin section findings. The study also determined the sensitivity, specificity, false negative rate and the accuracy of our technique.

MATERIALS AND METHODS

This study was carried out following the approval of our Institutional Research Ethics Committee. It is a cross sectional, descriptive, retrospective study using archival histopathological material of frozen sections and final paraffin sections slides of sentinel lymph nodes.

All breast cancer patients from our institution who underwent intraoperative sentinel lymph nodes frozen section analysis over a period of 4 years were included in this study.

The histological slides of frozen section and its corresponding paraffin section of all selected cases were retrieved from the department archives and were reviewed by two pathologists (S.H., L.S.K.). The size of the sentinel lymph node metastasis was assessed and categorised into isolated tumour cells, micrometastasis and macrometastasis as recommended in AJCC cancer staging manual.[13] A review of the original pathology reports for each case was also performed. Information regarding histological type of tumour, tumour grade and tumour size were retrieved from the reports.

The case was categorised as false negative when the intraoperative frozen sections diagnosis was reported as negative for metastatic tumour but the subsequent paraffin section was noted to have macro or micrometastases. This is either because metastatic tumour did not appear on the initial frozen sections (sampling or technical error) or was only identified retrospectively (interpretative error). A negative frozen section that showed isolated tumour cells on subsequent paraffin sections were not classified as false negative as they are staged as node negative, pN0(i+).

All the data were tabulated and processed using SPSS 20.0. Standard computation of sensitivity, specificity, false negative rate, accuracy, positive predictive value and negative predictive value were calculated, together with their confidence intervals at 95% (Wilson score).

RESULTS

A total of 82 patients underwent intraoperative frozen section analysis for axillary sentinel lymph nodes during the four-year period (2012-2015). The median age of the study population was 55 years old (range 26–83).

Of the 82 cases, 77 patients underwent both breast surgery and intraoperative frozen section sampling of the lymph node in our institution. The other 5 patients had only frozen section lymph node sampling at our centre after the definitive breast surgery was done elsewhere. Thus, for these five cases, the tumour grade and stage were not available (Table 1). Among the 77 cases, 69 cases were invasive carcinoma and eight cases were pure DCIS (10.4%). 60 out of 69 cases (77.9%) were diagnosed as invasive carcinoma, no special type (NST). The other nine cases were mucinous carcinoma (4 cases, 5.2%), medullary carcinoma (2 cases, 2.6%), invasive lobular carcinoma (1 case, 1.3%), encapsulated papillary carcinoma (1 case, 1.3%) and adenoid cystic carcinoma (1 case, 1.3%).

Using the modified Bloom-Richardson grading system for invasive carcinoma, 25/69 (36.8%) cases were categorised as grade 1, 30/69 (44.1%) cases grade 2, 13/69 (19.1%) cases grade 3 and one case was not graded due to lack of information. As for tumour staging of the 77 cases who underwent breast surgery in our institution, 8/77 (10.4%) cases were pTis, 34/77 (44.2%) cases were pT1, 32/77 (41.5%) cases were pT2 and only 3 (3.9%) cases were

TABLE 1: Clinicopathological characteristic of study population

Tumour Size of Carcinoma	**n (%)**
pTis	8 (10.4%)
pT1a	3 (3.9%)
pT1b	9 (11.7%)
pT1c	22 (28.6%)
pT2	32 (41.5%)
pT3	3 (3.9%)
Total	**77 (100.0%)**
Histology Subtype of Carcinoma	
Invasive carcinoma, non-otherwise specified (NST)	60 (77.9%)
Mucinous carcinoma	4 (5.2%)
Medullary carcinoma	2 (2.6%)
Invasive lobular carcinoma (ILC)	1 (1.3%)
Encapsulated papillary carcinoma	1 (1.3%)
Adenoid cystic carcinoma	1 (1.3%)
Ductal carcinoma-in-situ (DCIS)	8 (10.4%)
Total	**77 (100.0%)**
Tumour Grade of Invasive Carcinoma [a]	
Grade 1	25 (36.8%)
Grade 2	30 (44.1%)
Grade 3	13 (19.1%)
Total	**68 (100.0%)**

[a] Grade was not available in 1/69 case of invasive carcinoma

pT3. The clinicopathological characteristics are summarised in Table 1.

The mean number of axillary sentinel lymph node harvested was 2.3 per case (range 1–7). A total of 13/82 cases (15.9%) reported as positive on frozen sections were found to be truly positive on subsequent paraffin sections (Table 2). Of these 13 true positive cases, one case showed isolated tumour cells (Fig 1. A & B), five cases showed micrometastases (Fig 1. C & D) and seven cases showed macrometastases (Fig 1. E & F). All positive sentinel lymph node cases were seen in patients with invasive carcinoma, no special type (NST) with the exception of one case of invasive lobular carcinoma (ILC). The latter showed presence of micrometastasis on frozen sections (Table 2).

There were no false positive cases, however, there were two out of 82 (2.4%) cases which showed false negative results. These cases were reported as negative on frozen section but final paraffin sections showed presence of micrometastasis in one case and macrometastasis in another. Statistical analysis showed the sensitivity and specificity of intraoperative sentinel lymph node frozen section assessment in our centre was 86.7 and 100% respectively. The false negative rate was 13.3% and the accuracy was 97.5% (Table 3).

There were three cases of sentinel lymph nodes displaying isolated tumour cells, one of which was identified on the initial frozen sections (Fig 1. A&B) while the other two were only seen on the paraffin sections. These latter two cases were included under the category of true negative intraoperative frozen sections and stage as node negative, pN0 (i+).

Review of the false negative and inconclusive cases

In both false negative cases, the malignant cells were only present on subsequent paraffin sections and were not seen in the initial frozen sections. This is an inherent technical limitation of intraoperative frozen sections. Both cases showed metastatic foci within the lymph node parenchyma without subcapsular space involvement (Fig 1. G & H).

TABLE 2: Histological characteristic of cases with positive sentinel lymph node

	True Positive	False Negative
Histology Subtype		
Invasive carcinoma, non-otherwise specified (NST)	12	2
Invasive lobular carcinoma (ILC)	1	0
Total	**13**	**2**
Tumour Size		
pTis	0	0
pT1a	0	0
pT1b	2	0
pT1c	2	1
pT2	7	1
pT3	2	0
Total	**13**	**2**
Tumour Grade		
Grade 1	5	1
Grade 2	6	0
Grade 3	1	1
No data	1	0
Total	**13**	**2**
Metastatic size		
Isolated tumour cells (ITC)	1	0
Micrometastasis	5	1
Macrometastasis	7	1
Total	**13**	**2**

TABLE 3: Comparison of intraoperative frozen section sentinel lymph node analysis and final paraffin diagnosis

		Final paraffin diagnosis		
		Positive for malignancy	**Negative for malignancy**	**Total**
Intraoperative frozen section analysis	Positive for malignancy	13	0	13
	Negative for malignancy	2	64	66
	Total	15	64	79 [a]
	Sensitivity, %			86.7 (95% CI, 62.1% to 96.3%)
	Specificity, %			100 (95% CI, 94.3% to 100%)
	Positive predictive value, %			100 (95% CI, 77.2% to 100%)
	Negative predictive value, %			97.0 (95% CI, 89.6% to 99.2%)
	Accuracy, %			97.5 (95% CI, 91.2% to 99.3%)
	False negative rate, %			13.3

[a]The frozen section analysis is inconclusive in 3 out of 82 cases thus excluded from calculation

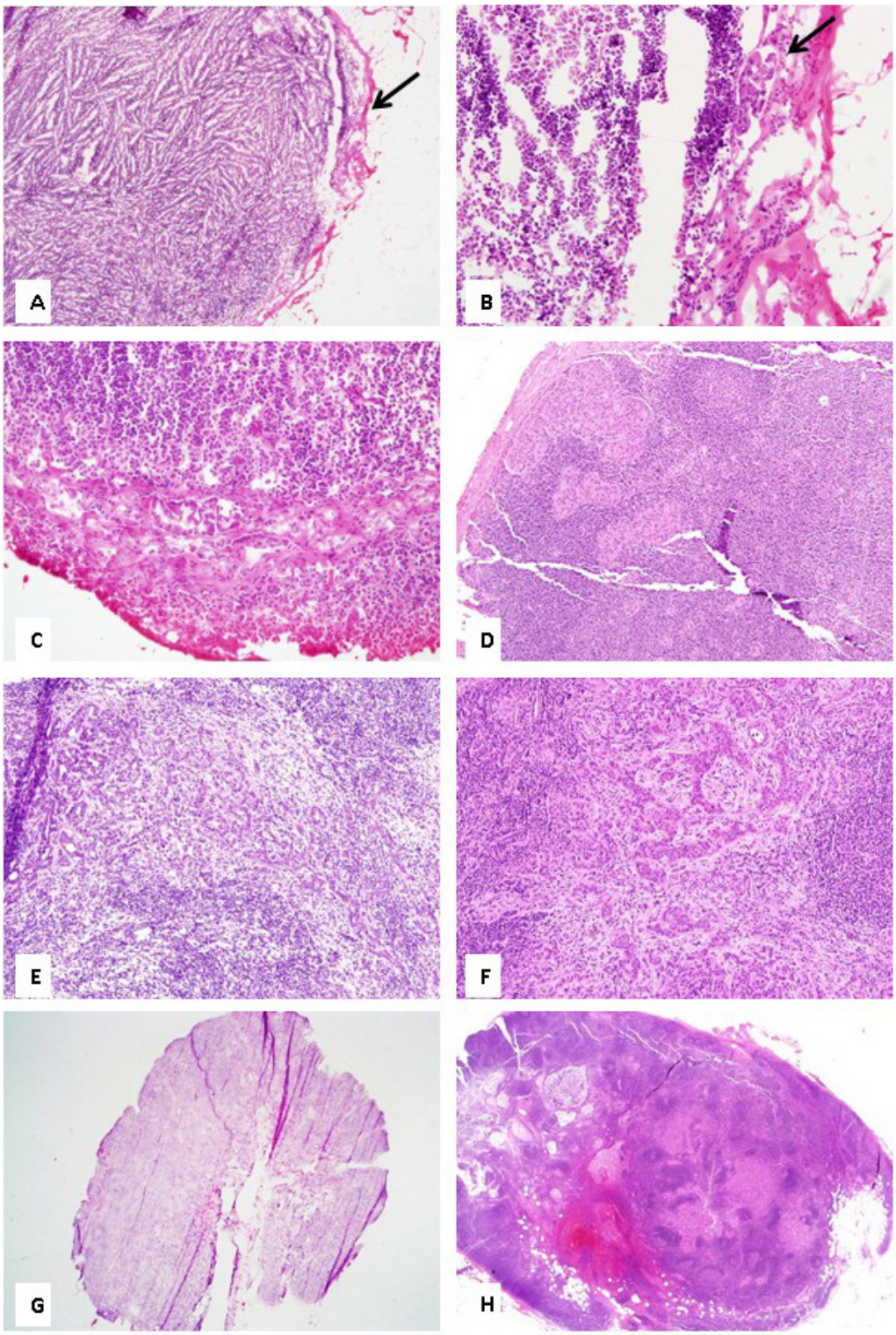

FIG. 1: (A) Metastatic isolated tumour cells in frozen section (arrow) in low (H&E, x40) and (B) high magnification (H&E, x200). (C) Micrometastasis in frozen section (H&E, x200) and (D) its final paraffin section (H&E, x100). (E) Macrometastasis in frozen section (H&E, x100) and (F) final paraffin section (H&E, x100). (G) False negative frozen section without obvious metastasis (H&E, x12.5) with (H) macrometastasis seen on the deeper paraffin section (H&E, x12.5).

In three out of the 82 cases (3.7%), the frozen section diagnoses were not conclusive; one was interpreted as suspicious for malignancy, while the others were described as atypical cells present. All these cases were found to be negative in the final paraffin sections. The results are summarised in Table 3.

Among the three inconclusive cases, two cases showed extensive ice crystal and sectioning artefacts. The first case consisted of one lymph node with seven levels examined, the second case consisted of six lymph nodes with total of 26 levels examined and the third case consisted of four lymph nodes with total of 32 levels examined. The third case showed presence of overlapping plump endothelial cells within the paracortex in one level of the frozen section, which was interpreted as indeterminate for malignancy during the initial assessment.

DISCUSSION

We presented a single institutional experience of intraoperative frozen section analysis for axillary sentinel lymph node in 82 breast cancer patients. The mean number of axillary sentinel lymph node was 2.3/patient, comparable to previous studies which showed a range between 1.8 to 2.6.[14]

Our intraoperative analysis findings are in keeping with most published data. This study showed the test sensitivity was 86.7%. Review of the literature showed that the sensitivity of the intra-operative frozen section analysis technique varies between 52% and 89%.[15] The test accuracy in our study was high (97.5%) and the test was also highly specific (100%). Previous meta-analysis showed the test accuracy ranging from 88 to 96%.[15]

There was no false positive case in our study. The false negative rate of our study was 13.3%. Internationally, false negative rates of intraoperative frozen section for axillary sentinel lymph node ranges from 7 to 56%.[15,16] The wide variability of the test sensitivity and false negativity are partly due to different practices and protocols in different institution.[14,17,18] These include the use of multilevel sectioning, concurrent imprint cytology and intraoperative immunohistochemistry study (IHC). In our institution, all the sentinel lymph nodes received were submitted for assessment. They were subjected to multilevel sectioning on the initial frozen sections, as well as the subsequent paraffin tissue blocks until the tissues were exhaustive. Immunohistochemistry study with cytokeratin was performed on one of the paraffin sections.

Both false negative cases in our study were due to sampling error. In our institution, a lymph node measured more than 5mm was sliced at 5mm interval before being submitted entirely and lymph node that measured less than 5 mm was submitted entirely. There are studies that recommend to serially section lymph nodes that are > 5mm at 2mm interval and lymph node < 5mm is bisected, to reduce false negative rate.[14,15,19]

There are also studies that showed the combination of frozen section with haematoxylin & eosin (H&E) and IHC raised the sensitivity of intraoperative consultation from 73.5% with H&E alone to 83.7% using the combined methods. However, the increased sensitivity was mainly due to the detection of micrometastasis, which was from 35% with H&E alone to 55% when combined with intraoperative IHC.[8] This protocol was laborious and time consuming and the biological significance of micrometastasis was debatable. The IBCSG 23-01 l and ACOSOG Z0011 trials showed that axillary lymph node dissection in sentinel lymph node micrometastasis was no longer indicated as it did not result in added survival benefit.[20,21] Therefore, intraoperative IHC for sentinel lymph nodes was not widely applicable.

Positive intraoperative sentinel lymph node predicted the likelihood of non-sentinel lymph node metastasis (38.2% vs 9.5%).[22] A positive frozen section analysis of sentinel lymph node which is usually performed during the same operative setting as the breast tumour excision or mastectomy can guide the surgeon to perform an immediate axillary lymph nodes dissection in the same surgery. This will effectively reduce the number of patients going for second axillary clearance surgery at different time.[9,10] In our study, all the 13 patients reported as positive sentinel lymph node frozen section analysis underwent non-sentinel lymph node dissection during the same operative settings with an average of 16.7 lymph nodes removed per case. Five out of the 13 cases (38.5%) yielded further non-sentinel lymph node metastasis, which is comparable to the published range of 40-60%.[23] However, only one of the cases showed a change from stage pN1 to pN2. All the other cases with axillary lymph node metastasis had three or less positive nodes in total.

One of the two false negative cases underwent secondary axillary lymph node dissection. The additional lymph nodes from second surgery did not show any further metastasis.

In this study, we also observed that some cases with negative intraoperative sentinel lymph node analysis underwent additional non-sentinel lymph node dissection. None of these cases showed presence of additional nodal metastasis. The reason for additional non-sentinel lymph node dissection was occasionally described in some studies. It could occur when the surgeon noted other clinically suspicious lymph node that was not radiolabeled or dyed during the initial mapping.[14]

Three cases in our study were inconclusive on intraoperative frozen section analysis (3.7%) due to the limitation by artefacts despite multiple level sectioning. The deferral rate for general intraoperative consultation is about 4.6%.[24] One study described the deferral rate for sentinel lymph node frozen section assessment in breast cancer is 0.67%.[15]

The status of axillary sentinel lymph node is prognostically important as the overall survival was shorter in patients with sentinel lymph node metastasis.[25] However, the approach to intraoperative frozen section analysis of sentinel lymph node may be changing in some early breast cancer patients due to the recent studies. In ACOSOG Z0011 trial, it was reported that in selected early stage breast cancer patients with positive sentinel lymph nodes, there was no significant difference in 10 years loco-regional recurrence, recurrence free survival or overall survival among patients whether non-sentinel lymph node dissection was performed.[26,27] This leads to reduce use of intraoperative frozen section for sentinel lymph nodes and deferral of its analysis on final paraffin sections.[28] A survey also reported that 21% of surgeons used fewer intraoperative frozen sections after the ACOSOG Z0011 trial.[29]

Generally, patients are not indicated for further non-sentinel axillary lymph node dissection in the absence of sentinel lymph node metastases. However, further studies are needed to identify the characteristic of sentinel lymph node-positive patients who will benefit from further non-sentinel axillary lymph node dissection. One such study is the recently initiated study (SENOMAC) that aim to evaluate the need of completion axillary lymph node dissection in sentinel lymph node positive breast cancer patients. This study has included intraoperative frozen sections as one of its study parameters. The results of this study may influence future management of the axillary lymph nodes in breast cancer patients.[30]

CONCLUSION

Intraoperative frozen section analysis for axillary sentinel lymph node is accurate and specific. False negative intraoperative consultation on sentinel lymph node was mostly due to sampling error. An understanding of limitation of frozen section analysis with diligent evaluation of frozen section specimen will be beneficial in improving its interpretation. The pathologist's experience and training are also paramount in increasing the accuracy of the analysis. A recommendation to serially section lymph nodes that are > 5mm at 2mm interval and lymph node < 5mm bisected to decrease this error is proposed.

Conflict of interest: The authors declared that there was no conflict of interest

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