



Efficacy of frozen section in sentinel lymph node biopsy in early breast cancer – An Australian single-centre experience

Elan Novis^{a,*}, Tae Jun Kim^a, Chahaya Gauci^a, Jasmine Mui^a, Yijun Gao^a, Natalia Garibotto^{a,b}

^a Department of Breast Surgery, St George Hospital, University of New South Wales Clinical School, Kogarah, NSW, Australia

^b St George Private Hospital, Kogarah, NSW, Australia

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ABSTRACT

Introduction: Sentinel lymph node biopsy (SLNB) is the standard of care for axillary staging in patients with clinically lymph node negative early breast cancer, reducing the need for axillary lymph node dissection (ALND) and its associated risks. Intra-operative frozen section is a method of rapid pathological assessment of the sentinel node to identify the presence of metastatic disease and potentially avoid the need for a second operation in patient who will require an axillary lymph node dissection.

Methods: A retrospective review of a prospectively collected breast cancer database was performed. All patients with breast cancer who underwent SLNB and/or ALND at our institution, between May 1st 2017 to June 1st 2022 were identified. There were 565 patients who were included in the study.

Results: Intra-operative frozen section was able to accurately identify 71% of patients who had macrometastasis in their sentinel lymph node, thus allowing them to immediately proceed to ALND and avoid a second operation. In patient who had a false negative frozen section result, only 6.5% required ALND. The majority of false negative results were due to isolated tumour cells or micrometastasis, and therefore would not have required further intervention.

Conclusion: Intra-operative frozen section of sentinel lymph node biopsy in breast cancer is useful in reducing the need for a second operation, allowing staging of the axilla to occur more efficiently and with high diagnostic accuracy.

Introduction

Sentinel lymph node biopsy (SLNB) is the standard of care for axillary staging in patients with clinically lymph node negative early breast cancer, reducing the need for axillary lymph node dissection (ALND) and its associated risks [1]. ALND is associated with complications and morbidity such as lymphoedema, nerve injury, decreased upper limb movement, seroma formation and infection, which can affect quality of life after surgery and delay commencement of adjuvant therapies [2].

SLNB allows the surgeon to determine which patients are unlikely to have lymph node metastasis and thus avoid these risks. The downside is that the final histopathological results of the SLNB often take a number of days to return. Therefore if the biopsy is positive for metastases, the ALND that is required is delayed, further delaying adjuvant therapies and inconveniencing the patient. To overcome this, in our institution we have implemented routine intraoperative frozen section (FS) for all SLNB to make an immediate decision whether to proceed to ALND and

thus reduce the possibility of requiring a second operation.

The management of the axilla in early breast cancer has undergone significant shifts in recent years following a number of randomised control trials which aim to de-escalate axillary surgery in this patient population [3–5]. These studies have demonstrated that in patients undergoing breast-conserving surgery with TNM staging T1 and T2 clinically node-negative breast cancers [6], who will receive adjuvant whole breast irradiation, ALND can be avoided if no more than two sentinel nodes are positive for metastatic disease. 10-year follow-up studies have demonstrated a non-inferior disease-free survival in these patients who do not proceed to ALND [5,7–8]. A criticism of the 2011 study was that the adjuvant radiotherapy regime given to patients was not standardised and included the axilla in the radiotherapy field. A follow up study, POSNOC is a UK-ANZ multicentre, non-inferiority, randomised trial comparing systemic therapy alone with systemic therapy plus Axillary Treatment (Axillary radiotherapy or ALND) for women with ≤ 2 macrometastases at SLNB [9]. This study, which has

* Corresponding author at: St George Hospital, gray St Kogarah NSW 2217, Australia.

E-mail address: elan.novis@health.nsw.gov.au (E. Novis).

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finished recruiting but is awaiting accrual of the 5year follow up data, aims at answering the question of treatment effect of the axillary radiotherapy in this population of patients.

However, questions still remain about the management of elderly and young patients, those with other high risk features such as extra-nodal tumour extension or those undergoing mastectomy [10]. Therefore while the indications for ALND are steadily decreasing, the identification of positive axillary lymph nodes is still an important part of the surgical management of early breast cancer.

The aim of this study is to demonstrate that intra-operative frozen section is accurate in determining the presence of lymph node metastasis in early breast cancer and can prevent the need for a second operation if ALND is required.

This article was previously presented as a poster abstract at the 2023 Royal Australasian College of Surgeons Annual Scientific Congress in May 2023.

Method

Patient selection

A retrospective review of a prospectively collected breast cancer database was performed. All patients with breast cancer who underwent SLNB and/or ALND at our institution, between May 1st 2017 to June 1st 2022 were identified. All patients had clinically negative axillary lymph nodes. There were 128 patients who were excluded due to proceeding directly to ALND, known metastatic disease, clinically node-positive disease, or were unable to localise a sentinel lymph node on lymphoscintigraphy. There were 565 patients who were included in the study.

Identification of sentinel lymph nodes

All patients had SLNB at the time of their primary breast cancer surgery. Patients underwent preoperative technetium 99 (Tc) sulphur colloid lymphoscintigraphy to identify the draining axillary sentinel lymph node. Tc99 sulphur colloid was injected either peritumorally, periareolar or at the previous surgical site. This was performed either on the morning of surgery or in the late afternoon the day before surgery depending on the timing of their operation. Those who did not localise a sentinel lymph node on preoperative lymphoscintigraphy, underwent level 1 axillary node sampling and thus were excluded from the study.

Intraoperatively, the sentinel lymph node was identified using a gamma probe with or without patent blue dye depending on surgeon preference. The exclusion for use of patent blue dye was due to risk of anaphylaxis. Any lymph node that was identified as positive by the gamma probe, or stained blue was excised and sent for FS as a fresh specimen. Part of the specimen was kept separate and fixed in formalin for formal histopathological (HP) assessment. The FS was assessed by a consultant pathologist (a fellow of the Royal College of Pathologists Australasia) and reported to the surgeon intraoperatively.

Data collection

FS results were compared with HP results to determine if they correlated (true positive or true negative), or whether they were discordant. If discordant, the result was stratified according to whether the frozen section was an upgrade or downgrade in the result. Upgraded results were further divided into those that went from negative to isolated tumour cells (ITC), negative to micrometastases, micrometastases to macrometastases, or negative to macrometastases.

Macrometastases were defined as breast carcinoma deposit of greater than two millimetre (>2 mm). Micrometastases - containing more than 200 cancer cells and less than 2 mm. Isolated tumour cells (ITC) are clusters of cancer cells measuring less than 0.2 mm or a single tumour cell. Macrometastases and micrometastases are formally known as positive lymph nodes.

Results

Patient characteristics

Of the 565 patients who were included in the study, 99.3% were female, median age was 61 years (range 24 to 92) and median ASA score was 2. The median number of lymph nodes excised was 2

The primary histopathology of the examined specimens are summarised in Table 1. The most common primary pathology was invasive ductal carcinoma (64.8%), followed by invasive lobular carcinoma (11.5%), and mixed ductal and lobular carcinoma (7.4%).

Difference in frozen section and histopathology

There were a total of 109 (19.3%) patients who had discordance between FS and HP results as summarised in Table 2.

From FS there were 66 (11.7%) true positive results and 390 (69.0%) true negative results. 108 (19.1%) patients had an upgrade on HP from a negative FS result, 9 of these were an upgrade from micrometastases to macrometastases, and 18 from node negative to macrometastases (1.6%, 3.2% respectively). These 27 (4.8%) were considered clinically significant in missed opportunity for simultaneous ALND.

Of the patients with a negative FS result, 37 (37.4%) patients were found to have ITC, 44 (44%) patients with micrometastases

There was one patient (0.2%) who was identified as a false positive. FS identified macrometastases which was identified to be negative for malignancy on HP. The positive cancerous tissue was part of the axillary tissue, not a lymph node.

The sensitivity and specificity of FS in detecting macrometastasis was calculated as 71.0% and 99.8% respectively, with a positive predictive value (PPV) 98.7% and negative predictive value (NPV) 87.3%.

Only 2 patients (0.36%) had macrometastases on FS but did not proceed to immediate ALND due to age and comorbidities. They had confirmed macrometastases on HP.

Proceeded to axillary lymph node dissection

64 patients (11.3%) had macrometastases on FS and proceeded direct to ALND in the same operation. There was 1 patient who had a false positive on FS and underwent ALND as mentioned previously.

Of the 64 patients who proceeded to ALND, 23 (35.9%) had no further positive lymph nodes

Of the 108 patients who had an upgrade on HP but negative FS, only 7 (6.5%) patients proceeded to ALND after multi-disciplinary team discussion.

Table 1

Primary breast histopathology subtypes in patients undergoing SLNB.

Primary histopathology	Number of patients	Percent (%)
Invasive Ductal Carcinoma	366	64.8
Invasive Lobular Carcinoma	65	11.5
Invasive Carcinoma with Mixed Ductal and Lobular Differentiation	42	7.4
Ductal Carcinoma in situ	28	5.0
Invasive Carcinoma with Micropapillary Features	14	2.5
Invasive Carcinoma with Tubular Features	13	2.3
Invasive Mucinous Carcinoma	12	2.1
Invasive Papillary Carcinoma	14	2.5
Mixed Invasive Mucinous and Papillary Carcinoma	4	0.7
Invasive Carcinoma with Medullary Pattern	3	0.5
Invasive Metaplastic Carcinoma	2	0.4
Atypical Ductal Hyperplasia	1	0.2
Lobular Carcinoma in situ	1	0.2
Total	565	100.0

Table 2
Difference in frozen section result and final histopathology of SLNB.

Difference between frozen section and histopathology results	Number of patients	Percentage (%)
Negative upgraded to Isolated Tumour Cells	37	6.5
Negative Upgraded to Micrometastasis	44	7.8
Micrometastasis upgraded to Macrometastasis	9	1.6
Negative Upgraded to Macrometastasis	18	3.2
False Positive	1	.2
True Negative	390	69.0
True Positive	66	11.7
Total	565	100.0

Discussion

Intra-operative frozen section was able to accurately identify 71% of patients who had macrometastasis in their sentinel lymph node, thus allowing them to immediately proceed to ALND and avoid a second operation. In patient who had a false negative frozen section result, only 6.5% required ALND. The majority of false negative results were due to isolated tumour cells or micrometastasis, and therefore would not have required further intervention.

FS was first described by Wilson in 1905 [11]. This technique is now widely used in many surgical specialties to rapidly identify patients with nodal metastases who may then directly proceed to a more extensive lymph node dissection as a single stage procedure. Benefits of FS include immediate identification of positive sentinel lymph nodes allowing the patient to proceed to ALND, thus avoiding the risk of further anaesthetics, reducing hospital costs. It also provides an assessment of the size of any metastases which aids in the decision making about proceeding the ALND.

FS has been questioned in other studies, as a result of the reduced indication for ALND based on ACOSOG Z0011 trial as well as proposed increased costs and risk of tissue loss preventing final pathological diagnosis [12,13]. We would argue that the FS procedure does not increase operative time if performed before the excision of breast lesion, as the result is often available by the time the breast lesion is excised. In our institution, FS results are generally processed efficiently and available prior to the conclusion of surgery, therefore there was generally no increase in overall anaesthetic time.

Published sensitivity and specificity rates for detection of lymph node metastasis from intra-operative FS are 75% and 99% respectively [14]. When detecting macrometastasis, FS sensitivity increases to 90%. False negative rates have been reported between 5.5% - 43%, which probably reflects the variability in technique and expertise across institutions, as well as the size of the metastases, with false negative rates being low for macrometastasis and high for micrometastatic disease [15]. Our results reflect a similar rate with a sensitivity of 71% and specificity of 99.8%, with a false negative rate for macrometastasis of 5.4%. In terms of micrometastasis and isolated tumour cells, FS was unable to identify this in 14.3% of patients in our study. Given these patients would not benefit from ALND [16], the clinical implications of this are questionable.

Since the ACOSOG Z0011 trial [4], there has been a decline in the use of FS for assessment of sentinel lymph nodes given that many surgeons are now omitting ALND for patients with T1–2 disease with one or two positive lymph nodes, who will otherwise be undergoing whole-breast irradiation [17]. In patients with micrometastasis, ALND is omitted. We propose that FS can still have a role in patients who do not meet Z011 criteria potentially preventing the need for a second surgery in 68.8% of patients who required ALND. This may reduce valuable operating waiting lists and improve efficiency in implementing adjuvant therapies.

The limitations of this study are that both patients who underwent

mastectomy and breast conserving surgery were included, therefore the usefulness of FS assessment cannot be differentiated between the two. Also the T-stage of the primary tumour was not recorded therefore the need for ALND based on the ACOSOG Z0011 criteria cannot be assessed.

Conclusion

Intra-operative FS of sentinel lymph node biopsy in breast cancer is useful in reducing the need for a second operation, allowing staging of the axilla to occur more efficiently and with high diagnostic accuracy. Given the clinical need for ALND is reducing following recent trials in patients undergoing breast-conservation surgery, further studies focused on the use of intra-operative FS to identify patients who meet this criteria for omission of ALND are needed.

Author contributions

Elan Novis: Writing original draft, review and editing. **Tae Jun Kim:** Conceptualization, Writing original draft and editing. **Chayaha Gauci:** data analysis and editing. **Jasmine Mui:** data collection. **Yijun Gao:** data collection. **Natalia Garibotto:** writing review, supervision and editing

Ethical approval

Human research and ethics approval was waived by the South Eastern Sydney Local Health District Human Research and Ethics Committee

Disclosure statement

No conflicts of interest to disclose

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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