

Reconsidering the Need for Intraoperative Frozen Section in Sentinel Lymph Node Biopsy for Early Breast Cancer in Bahrain

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ABSTRACT: Objectives: Frozen section is performed in sentinel lymph node biopsy (SLNB) for early breast cancer to prevent a second surgery, but it has certain disadvantages. Several trials have demonstrated the oncological safety of avoiding axillary dissection in patients with 1–2 positive nodes. This study aimed to assess the need for frozen section during SLNB in early breast cancer. **Methods:** This retrospective study included patients with early-stage clinically node-negative breast cancer who underwent SLNB with frozen section at Salmaniya Medical Complex, Manama, Bahrain, between October 2021 and September 2023. Patients who had neoadjuvant chemotherapy, cT3–4 tumours, ductal carcinoma *in situ*, occult breast cancer and previous breast cancer were excluded. **Results:** A total of 147 patients underwent breast cancer surgery with SLNB using frozen section. The sensitivity of frozen section was 84.6%, and the false-negative rate was 15.4%. Furthermore, 4.8% underwent immediate axillary dissection. In the remaining cases, there were only 1–2 positive sentinel nodes, and axillary dissection was omitted. Multifocal or multicentric disease was significantly associated with <3 positive sentinel nodes (71.4% versus 15.0%; $P = 0.005$). Patients with an indication for axillary dissection were also more likely to have tumours with lymphovascular invasion compared to patients with ≥ 3 positive sentinel nodes (85.7% versus 17.1%; $P = 0.001$). **Conclusion:** There was no indication for frozen section is needed in most patients with early breast cancer. Routine frozen section is unnecessary during SLNB, and permanent section alone may be sufficient without compromising overall standard of care.

Keywords: Sentinel Lymph Node Biopsy; Frozen Sections; Axilla; Breast Cancer; Bahrain.

ADVANCES IN KNOWLEDGE

- Sentinel lymph node biopsy (SLNB) is routinely performed at Salmaniya Medical Complex, Manama, Bahrain, using frozen section to prevent reoperation for axillary lymph node dissection (ALND). However, it is associated with a sensitivity of 84.6% and false-negative rate of 15.4%.
- Results showed that frozen section during SLNB only prevented a second operation in less than 5% of cases. Therefore, SLNB with permanent section alone may be sufficient.
- Only patients with multifocal or multicentric disease and tumours with lymphovascular invasion may benefit from frozen section as they are more likely to have ALND, thus preventing a second operation.

APPLICATION TO PATIENT CARE

- These findings will help establish a local policy to replace frozen section with permanent section in most cases, thereby reducing prolonged operations and associated costs without impacting the overall standard of care.
- The need for frozen section should be limited to patients undergoing prolonged procedures, cases that underwent neoadjuvant chemotherapy and those that are at high risk for general anaesthesia or a second operation.

AXILLARY LYMPH NODE STATUS IS REGARDED as one of the most important prognostic factors for patients with early breast cancer, particularly for adjuvant therapy decisions. Over the last 2 decades, sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection (ALND) as the standard of care for axillary staging in early breast cancer and has reduced patient morbidity without compromising oncological outcomes.¹ Current indications for SLNB in breast cancer include cT1–2 invasive tumours with clinically negative axilla.² The American College of Surgeons Oncology Group Z0011 (ACOSOG Z011) trial reported that ALND is not

always indicated even in patients with up to 2 positive sentinel lymph nodes (SLNs) who were treated with breast-conserving surgery (BCS) and adjuvant radiation therapy.³ The International Breast Cancer Study Group 23-01 trial demonstrated that micrometastases are not an indication for further ALND.⁴ The 'Axillary Mapping of the Axilla: Radiotherapy or Surgery?' (AMAROS) trial found that axillary radiotherapy may be a comparable alternative to ALND without the surgical morbidity of the latter.⁵ The rate of ALND has reduced globally because these trials have established the safety of omitting ALND in early breast cancer patients with limited axillary involvement.^{6,7}

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International guidelines recommend that each institution establish a policy on intraoperative assessment of SLNs or deferral to permanent section, with both approaches considered appropriate.^{2,8} SLNs are evaluated using intraoperative frozen section and permanent section. At Salmaniya Medical Complex, Manama, Bahrain, the healthcare providers routinely perform intraoperative frozen section analysis of SLNs to reduce the need for a second operation.⁹ However, frozen section is associated with low sensitivity, resulting in some patients who need staged ALND, along with greater psychosocial patient discomfort, need for experienced pathologists, prolonged operative time and increased healthcare costs.^{10,11} With the implementation of the ACOSOG Z011 and AMAROS trials in clinical practice, which recommend ALND only when more than 2 nodal metastases are found, there has been a significant decline in the use of frozen section in SLNB.¹² Several studies have questioned the benefit of frozen sections in early node-negative breast cancer and reported that permanent section alone may be sufficient in these cases.^{13–15} Thus, this study aimed to evaluate the need for intraoperative frozen section during SLNB in early-stage breast cancer patients and examine whether it confers additional benefit in terms of change in the surgical treatment plan.

Methods

This retrospective study was conducted at Salmaniya Medical Complex from October 2021 to September 2023. The pathology database was reviewed and patients were included if they had cT1-2 (up to 5 cm) invasive breast cancer and underwent breast cancer surgery (BCS or mastectomy) with SLNB using intraoperative frozen section. Patients who underwent neoadjuvant chemotherapy or had cT3-4 tumours were excluded. In addition, patients who (a) underwent surgery for ductal carcinoma *in situ*, occult breast cancer or local recurrence; (b) underwent SLNB without frozen section; (c) had upfront ALND; (d) did not have any axillary surgery; or (e) were diagnosed with axillary lymph node metastases preoperatively by core biopsy were excluded.

All patients were evaluated by mammography and ultrasonography of the breasts and axillae. If a suspicious lymph node was identified on imaging, an ultrasound-guided biopsy was performed to exclude nodal metastases. All patients with cT1-2N0 breast cancer underwent SLNB by a dual technique using radioisotope and blue dye. Intraoperative frozen section was performed in all patients by experienced pathologists. Each lymph node was bisected and sliced serially, perpendicular to its long axis. Frozen

section involved preparation using haematoxylin and eosin stain, followed by microscopic examination. The frozen section report was conveyed to the operating surgeon within 45 minutes. The remaining lymph node specimen was fixed in formalin to determine the final pathology. Additionally, the pathologist also examined this permanent section postoperatively. ALND was performed only if more than 2 SLNs were positive on the frozen section.

The following clinical and pathological tumour characteristics were collected and analysed: age at diagnosis, histological tumour type, tumour grade, tumour size, disease focality, lymphovascular invasion (LVI), oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) status, Ki67 index, number of SLNs retrieved, number of positive SLNs and number of those who had ALND. Clinicopathological factors were compared according to the number of metastatic lymph nodes and whether ALND was indicated using the Chi-squared and Fisher's exact tests. In addition, the study cohort was divided into 2 groups according to the need for axillary dissection: patients with less than 3 positive SLNs and those with at least 3 positive SLNs. Statistical analysis was performed using the SPSS software, Version 29.0 (IBM Corp., Armonk, New York, USA). *P* values less than 0.05 were considered to be statistically significant.

The study method was approved by the ethical committee of Government Hospitals Bahrain (#64-230054).

Results

The baseline characteristics of the study population are summarised in Table 1. A total of 147 patients with early breast cancer underwent SLNB with intraoperative frozen section at the institution over the study period. The median age was 58 (range: 26–92) years. Almost half (46.9%) of cases were cT1 tumours and the majority (82.3%) had invasive ductal carcinoma (IDC). Most patients had a single focus of disease, as only 17.7% had multifocal or multicentric tumours. BCS was performed in 56.5% of patients. The majority (61.9%) of tumours were reported to be grade 2. In terms of immunohistochemistry, most cases were found to be ER-receptor (90.5%) and PR-receptor (82.3%) positive. Moreover, 9.5% of tumours were HER2-positive, while 38.1% had a high Ki67 index of $\geq 20\%$ [Table 1].

The median number of lymph nodes harvested at SLNB was 3 (range: 1–5); 39 (26.5%) patients had a positive SLN on final pathology. Frozen section correctly identified nodal metastases (true-positive)

Table 1: Characteristics of patient with early-stage clinically node-negative breast cancer who underwent sentinel lymph node biopsy with frozen section (N = 147)

Characteristic	n (%)
Mean, median age in years (range)	56,58 (26–92)
Histology	
Ductal	121 (82.3)
Lobular	16 (10.9)
Other	10 (6.8)
cT stage	
T1a	2 (1.4)
T1b	18 (12.2)
T1c	69 (46.9)
T2	58 (39.5)
pT stage	
T1a	10 (6.8)
T1b	17 (11.6)
T1c	50 (34.0)
T2	70 (47.6)
pN status	
N0	108 (73.5)
N1mi	5 (3.4)
N1	29 (19.7)
N2	5 (3.4)
Tumour grade	
1	34 (23.1)
2	91 (61.9)
3	22 (15.0)
ER status	
Positive	133 (90.5)
Negative	14 (9.5)
PR status	
Positive	121 (82.3)
Negative	26 (17.7)
HER2 status	
Positive	14 (9.5)
Negative	133 (90.5)
Ki67 index	
<20	91(61.9)
≥20	56 (38.1)
Disease focality	
Unifocal	121 (82.3)
Multifocal or multicentric	26 (17.7)
LVI	
Present	30 (20.4)
Absent	117 (79.6)
Surgery	
BCS	83 (56.5)
Mastectomy	64 (43.5)

cT = clinical tumour stage; T1a = tumour ≤5 mm; T1b = tumour >5 mm and ≤10 mm; T1c = tumour >10 mm and ≤20 mm; T2 = tumour >20 mm and ≤50 mm; pT = pathological tumour stage; pN = pathological nodal stage; pN0 = no regional lymph node metastasis; N1mi = micrometastasis > 0.2 mm and ≤ 2 mm; N1 = metastasis in 1–3 nodes; N2 = metastasis in 4–9 nodes; ER = oestrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor-2; Ki67 = marker of proliferation Kiel 67; LVI = lymphovascular invasion; BCS = breast conserving surgery.

in 33 (22.4%) of cases. Overall, 114 patients had a negative frozen section result; however, 6 (5.3%) of these were found to be positive on permanent section. Nevertheless, these 6 false-negative cases only had 1–2 positive SLNs, with no indication for further axillary surgery. Notably, there were no false-positive cases. The sensitivity of frozen section was 84.6%, indicating a false-negative rate (false-negative rate [FNR]; 1 - sensitivity) of 15.4%. Out of the study cohort, 7 (4.8%) patients underwent immediate ALND, as they had at least 3 positive SLNs. In the remaining cases with positive frozen section results, ALND was omitted, in keeping with recommendations of the ACOSOG Z011 and AMAROS trials.^{2,4}

Overall, 140 (95.2%) patients had 0–2 positive SLNs and 7 (4.8%) had ≥3 positive SLNs. Multifocal or multicentric disease was more frequent in patients with ≥3 positive SLNs (71.4% versus 15.0%; $P = 0.005$). Patients with an indication for ALND also had a significantly greater proportion of tumours with LVI (85.7% versus 17.1%; $P = 0.001$). Compared to T1 tumours, those with T2 tumours were more likely to have ≥3 positive SLNs, but this did not achieve statistical significance ($P = 0.830$). Additionally, age, histological subtype, tumour grade, hormone receptor status, HER2 status, Ki67 index and type of breast surgery did not affect the number of positive SLNs [Table 2].

Discussion

Analysis of SLNs with intraoperative frozen section has been traditionally used to reduce the need for reoperation in patients with metastatic disease.⁹ This study found that the use of frozen section resulted in the prevention of 7 reoperations for ALND, which accounts for less than 5% of cases. Therefore, the routine use of frozen section does not necessarily prevent a second axillary surgery compared to SLNB with the sole use of permanent section. According to the ACOSOG Z0011 and AMAROS trials, an ALND is only indicated when 3 or more SLNs are positive for metastatic disease.^{3,5} For that reason, intraoperative frozen section analysis does not benefit patients with up to 2 nodal metastases.¹⁴ In the era of de-escalation of axillary surgery, the current need for intraoperative frozen section is controversial, with studies discouraging the routine use of frozen sections in early-stage breast cancer who satisfy ACOSOG Z0011 and AMAROS criteria and advocating the sole use of permanent section in these patients.^{15–18}

Even with routine frozen section, a delayed ALND may still be required if the frozen section result

Table 2: Clinicopathological factors associated with number of positive sentinel lymph nodes

Characteristic	Number of positive SLNs (%)		P value
	0–2 (n = 140)	≥3 (n = 7)	
Age in years			0.283
<50	47 (33.6)	4 (57.1)	
≥50	93 (66.4)	3 (42.9)	
Histology			0.558
Ductal	115 (82.1)	6 (85.7)	
Lobular	15 (10.7)	1 (14.3)	
Other	10 (7.1)	0 (0.0)	
T stage			0.830
T1a	9 (6.4)	1 (14.3)	
T1b	17 (12.1)	0 (0.0)	
T1c	48 (34.3)	2 (28.6)	
T2	66 (47.1)	4 (57.1)	
Tumour grade			0.711
1	33 (23.6)	1 (14.3)	
2	85 (60.7)	5 (71.4)	
3	22 (15.7)	1 (14.3)	
Disease extent			0.005
Unifocal	119 (85.0)	2 (28.6)	
Multifocal or multicentric	21 (15.0)	5 (71.4)	
LVI			0.001
Present	24 (17.1)	6 (85.7)	
Absent	116 (82.9)	1 (14.3)	
ER status			0.440
Negative	14 (10.0)	0 (0.0)	
Positive	126 (90.0)	7 (100.0)	
PR status			0.202
Negative	26 (18.6)	0 (0.0)	
Positive	114 (81.4)	7 (100.0)	
Ki67 index			0.328
<20	89 (63.6)	3 (42.9)	
≥20	51 (36.4)	4 (57.1)	
HER2 status			0.440
Negative	126 (90.0)	7 (100.0)	
Positive	14 (10.0)	0 (0.0)	
Surgery			0.511
BCS	79 (56.4)	4 (57.1)	
Mastectomy	61 (43.6)	3 (42.9)	

SLNs = sentinel lymph nodes; T = tumour stage; T1a = tumour ≤5 mm; T1b = tumour >5 mm and ≤10 mm; T1c = tumour >10 mm and ≤20 mm; T2 = tumour >20 mm and ≤50 mm; LVI = lymphovascular invasion; ER = oestrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor-2; Ki67 = marker of proliferation Kiel 67; BCS = breast conserving surgery.

is false-negative. The reported FNR of intraoperative frozen section in the literature ranges from 5% to 17%.¹⁹ In this retrospective review, the FNR was 15.4% when comparing frozen section to permanent section. In all the false-negative cases in this study, there were no more than 2 diseased nodes.

There are other important drawbacks to the routine practice of performing frozen sections. It

is a time-consuming procedure that prolongs the operative time under general anaesthesia, requires an experienced pathologist and is also costly.¹⁷ Moreover, the preparation process could result in permanent tissue loss, which could ultimately result in a change in the final diagnosis.¹⁴ Frozen sections are considered inferior to permanent sections, as they are difficult to interpret due to the limited applicability of IHC

for frozen sections.¹⁸ Other authors have reported that frozen section was not sufficient to exclude micrometastases.¹⁴ One study also found that frozen section may lead to uncertainty for general surgeons who do not specialise in breast cancer surgery, with unnecessary ALNDs being performed even with 1–2 metastatic nodes, and additional axillary surgery may have been avoided if frozen section was not performed.¹⁹

This study found an average of 3 SLNs retrieved per patient, with over 60% of cases removing at least 3 SLNs. This data is comparable to the optimal yield of SLNs during SLNB, as the number of SLNs is considered significant when at least two SLNs are excised.²⁰ An earlier study conducted at the same institution found that high tumour grade, ER-negativity, LVI and large tumour size were associated with SLN metastasis.¹¹ In this study, multifocality or multicentricity and the presence of LVI were the only variables associated with at least 3 positive SLNs, an indication for ALND. Therefore, in patients with multifocal or multicentric disease and cases with LVI, frozen section may be indicated to prevent reoperation for ALND. Furthermore, these findings also suggest that other variables, such as age, tumour size, tumour grade, histological subtype, hormone receptor status, HER2 amplification and Ki67 index, had no significant relationship with the number of positive SLNs. This indicates that the likelihood of performing immediate ALND is low, and frozen section may be omitted in the majority of these patients.

Imaging is important in terms of evaluation of the axilla and estimation of the nodal burden.¹⁵ Compared to ultrasound, magnetic resonance imaging (MRI) determines the extent of disease, reveals more axillary information such as enhancement of suspicious lymph nodes, can be used to compare bilateral axillae and is less operator-dependent.²¹ In addition, MRI provides a comprehensive view of the axilla, as the number of pathological axillary nodes is more important than detecting axillary metastasis.¹⁵ This is becoming increasingly essential today, because according to the recent National Comprehensive Cancer Network (NCCN) guidelines, SLNB can even be performed when biopsy results are positive with limited axillary lymph involvement on imaging.² The current authors routinely perform axillary ultrasound in all cases of newly diagnosed breast cancer at the institution, with ultrasound-guided biopsy for all patients with suspicious nodes. This increases the likelihood of detecting node-positive patients preoperatively. Moreover, during the study period, surgeons at this

institution still performed ALND for cases with positive axillary biopsy results as recommended by older NCCN guidelines (these patients were excluded from the study).

This study demonstrated that only a few reoperations for ALND were prevented by routine use of frozen section during SLNB. Even with frozen section, a second axillary surgery may be needed, indicating that SLNB without frozen section may not be inferior to the current practice of routine intraoperative frozen section in all patients with clinically node-negative early breast cancer. This practice of SLNB with only permanent section could reduce the financial burden of breast cancer surgery and increase its cost-effectiveness, without compromising the overall standard of care.¹⁹ In addition, a reduction in total operative time is expected.²⁰ Based on these data, the omission of frozen section during SLNB for most patients with cT1–2 early breast cancer is recommended. In patients with cT3–4 tumours and those who undergo neoadjuvant chemotherapy, this study recommends that frozen section should be performed at the time of SLNB, as detection of even a single positive SLN is an indication for ALND. Other indications for frozen section may include patients undergoing longer procedures, such as mastectomy with an implant or autologous tissue reconstruction, and those who are unfit for a second surgery or at high risk for general anaesthesia.

This study was subject to certain limitations including its retrospective nature, single institution experience and relatively small sample size. Despite earlier implementation of ACOSOG Z0011 trial criteria in practice, it was only in 2021 that the institution adopted the AMAROS trial criteria for omission of ALND in mastectomy patients with limited axillary involvement after it was incorporated into NCCN guidelines, which explains the 2-year study period. Despite these limitations, this study is important because it re-evaluates the role of intraoperative frozen section in SLNB for early breast cancer in Bahrain. To the best of the authors' knowledge, this study is the first from the Middle East to examine the role of frozen section in the era of ACOSOG Z0011 and AMAROS trials, which may influence other authors in the region to investigate the need for intraoperative assessment at the time of SLNB to implement a change in clinical practice. If frozen section is not performed, there is a small reoperation rate for second axillary surgery. Therefore, the findings suggest a larger prospective study to provide validity of SLNB in the context of permanent section alone.

Conclusion

In the era of de-escalation of axillary surgery, this study found that frozen section was not indicated for most patients with early clinically node-negative breast cancer. With a small rate of ALND, SLNB with permanent section alone may be sufficient, and frozen section may be avoided in most of these patients. Frozen section confers a small benefit in terms of changing the surgical treatment plan and is associated with false-negative results, increased financial burden and prolonged operations. Therefore, based on the findings, it is suggested that routine unnecessary intraoperative frozen section analysis during SLNB be omitted for patients with early breast cancer. SLNB with permanent section alone will help reduce healthcare costs and operative time, without a significant impact on the overall standard of care and quality of treatment.

AUTHORS' CONTRIBUTION

AZS, MH and HAA contributed to the study design. NFA and AHA were involved in the data collection. SJA and FAA performed the data analysis. The initial draft was prepared by AZS, NFA and AHA. MH and HAA critically revised the manuscript. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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