# Intraoperative Frozen Section Analysis of Sentinel Lymph Nodes in Breast Cancer Patients: A Meta-analysis and Single-Institution Experience

**Running title: Is Frozen Section of SLNs Accurate?**

Liang-Chih Liu, MD[*1,7], Julie E. Lang, MD[*1,5],
Ying Lu, Ph.D[2], Denise Roe, Dr.P.H.[8], Shelley E. Hwang, MD/MPH[1], Cheryl A. Ewing, MD[1], Laura J. Esserman, MD/MBA[1], Eugene Morita, MD[3],
Patrick Treseler, MD[4], Stanley P. Leong, MD[1, 6]

[1]University of California, San Francisco (UCSF) Department of Surgery and UCSF Helen Diller and Family Comprehensive Cancer Center (UCSF HDFCCC)
[2]UCSF Departments of Radiology and Biostatistics Core of UCSF HDFCCC, San Francisco, CA
[3]Department of Nuclear Medicine, UCSF, San Francisco, CA
[4]Department of Pathology, UCSF, San Francisco, CA
[5]Department of Surgery, University of Arizona, Tucson, AZ
[6]Department of Surgery, California Pacific Medical Center and Research Institute, San Francisco, CA
[7]Department of Surgery**,** China Medical University Hospital, Taichung, Taiwan, Republic of China
[8]Department of Epidemiology and Biostatistics, School of Public Health; Section of Biometry, Arizona Cancer Center, University of Arizona, Tucson AZ
[*]Dr. Liu and Dr. Lang contributed equally to this work.

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**Corresponding author and reprint requests:** Stanley P. Leong, MD, Department of Surgery, California Pacific Medical Center and Research Institute, 2340 Clay Street, 2nd Floor, San Francisco, CA 94115.
Email:leongsx@cpmcri.org; Phone: 415-600-3800; FAX: 415-600-3865
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**Condensed abstract:** We performed both a single institution and meta-analysis evaluating the accuracy of intraoperative frozen section (IFS) of SLNs during breast cancer surgery. IFS of SLNs is more reliable for detecting macrometastasis than for detecting micrometastasis or isolated tumor cell (Mi/ITC) deposits; it lacks sufficient accuracy to rule out Mi/ITC deposits.

## Abstract

**Background:** Accurate intraoperative pathologic examination of sentinel lymph nodes (SLNs) is necessary to avoid reoperations for patients with SLN-positive breast cancer. We sought to determine the accuracy of intraoperative frozen section of SLNs during breast cancer surgery.

**Methods:** In this retrospective study, we reviewed the records of 326 breast cancer patients who underwent intraoperative frozen section analysis (IFS) of SLNs at a single institution. We did a meta-analysis of 47 published

studies documenting results of IFS of SLNs in breast cancer patients.

**Results:** Sections stained with hematoxylin and eosin (H&E) showed metastasis in SLNs in 99 patients (30.4%): 61 had macrometastasis (MAM group) (> 2 mm), and 38 had micrometastasis (Mi) or isolated tumor cell (ITC) deposits (Mi/ITC group). The overall sensitivity of our institutional series was 60.6% (60/99); and the overall specificity, 100% (227/227). The sensitivity of IFS was significantly lower in the Mi/ITC group (28.9%) than in the MAM group (80.3%) ($p<0.0001$). Per our meta-analysis of published studies and our own data (47 studies, for a total of 13,062 patients who underwent selective sentinel lymphadenectomy [SSL] with IFS of SNLs), the mean sensitivity was 73%; the mean specificity, 100%. In our study, for the MAM group, the mean sensitivity was 94%; for the Mi/ITC group, 40%.

**Conclusions:** IFS of SLNs is more reliable for detecting MAM than for detecting Mi/ITC deposits. It lacks sufficient accuracy to rule out Mi/ITC deposits.

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## Background

Selective sentinel lymphadenectomy (SSL) has become a standard technique for accurately determining axillary lymph node status in breast cancer patients.[1-4] Numerous studies have reported and confirmed the high sensitivity and specificity of SSL in breast cancer patients.[5-18] Several studies reported that SSL has significantly minimized short-term morbidity and lymphedema, as compared with axillary lymph node dissection (ALND).[19-21]

Accurate sentinel lymph node (SLN) analysis requires coordinated efforts by a multidisciplinary team. If the SLN is found to be positive intraoperatively, the patient may be a candidate for immediate ALND. Intraoperative pathologic examination of SLNs is helpful to avoid reoperations for SLN-positive patients, thus sparing them an additional operation with its risks and additional costs.

Frozen section is the most common method of intraoperative evaluation, but no pathologic method has been standardized for SLN evaluation. Multilevel sectioning has been used for pathologic evaluation of SLNs; however, institutional protocols vary widely.[22,23] The 2005 American Society of Clinical Oncology (ASCO) guidelines for intraoperative evaluation of SLNs stated that, although IFS risks significant destruction of potentially diagnostic tissue, it may be the most desirable method with experienced teams of surgeons and pathologists.[24] The aim of this study was to determine the accuracy of IFS of SLNs during breast cancer surgery.

## Methods

### Patient selection

In this retrospective study, we reviewed the records of 326 consecutive patients treated for invasive breast cancer who underwent SSL with IFS at a single institution (the University of California, San Francisco [UCSF]) from November 1997 through April 2003. This study was approved by the institutional review board at UCSF. No patients were treated with neoadjuvant chemotherapy.

### Preoperative lymphoscintigraphy

The decision to use preoperative lymphoscintigraphy to identify the draining axillary SLNs was at the discretion of the operating surgeon. Technetium 99 sulfur colloid was injected either intradermally above the tumor, peritumorally, or at the surgical site of the previous biopsy. Patients underwent injection of radioisotope, with or without lymphoscintigraphy, either the morning of the surgery or in the late afternoon the day before surgery

### Intraoperative identification of SLNs

During the operation, the hand-held gamma probe (Neoprobe Corporation, Dublin, OH) was used to evaluate radioactive counts. Injection of Lymphazurin dye (Hirsch Industries, Richmond, VA) was at the surgeon's discretion.[25] A SLN was defined as a blue node and/or a node whose ex vivo radioactive count was ≥ 10% of the ex vivo radioactive count of the hottest lymph node. Any lymph node with ≥ 10% of the ex vivo radioactive count of the highest SLN was removed. Additionally, any clinically suspicious palpable nodes were removed and defined as sentinel nodes.[26]

**Pathologic evaluation**

The radioactive count of all SLNs removed was measured and documented. All SLNs were submitted to the pathology department and subjected to standard frozen section evaluation with 1 or 2 H&E-stained sections.

Tumor stage was determined using the 6th edition of the *AJCC [American Joint Committee on Cancer] Cancer Staging Manual*; permanent sections were stained with H&E, with or without immunohistochemistry (IHC), and consisted of a bisection of at least 3 levels at intervals of 40 to 100 μm.[27, 28] All nodal tissue specimens submitted for frozen section evaluation were resubmitted for permanent-section analysis (PSPA). Our protocol included 3 levels of IHC stains and 2 levels of H&E stains.[22, 23]

**Literature review**

We systematically searched PubMed from January 1997 through June 2008, using the keywords "breast cancer," "breast neoplasm," "frozen section," "sentinel lymph node," and "SLN." A single reviewer (LCL) selected the articles and extracted the data for analysis. References of included articles were searched for additional studies that met our inclusion criteria. We included all articles that reported sufficient data for cross-tabulation of the results of IFS of SLNs against (PSPA). We excluded all articles with missing statistical data (i.e., sensitivity, specificity). We also excluded all articles in languages other than English that were not available in translated form. All studies involving neoadjuvant therapy were excluded.

The data were collected on a per-patient basis, rather than per node examined. Our meta-analysis was applied to evaluate the accuracy of intraoperative frozen section evaluation.

**Statistical analysis**

Using the results of the PSPA, we calculated sensitivity, specificity, and positive and negative predictive values.

Because the numbers of patients with Mi and with ITC deposits were low, we combined them into the Mi/ITC group, in order to compare their results with those of the MAM group. We used Mantel-Haenszel and/or Chi Square statistics to compare the sensitivity, and accuracy for different tumor sizes, as well as to compare the sensitivity for detecting MAM and Mi/ITC. We considered $p < 0.05$ to be statistically significant.

Because different studies in a meta-analysis may have used different thresholds to define positive results, we used summary ROC (SROC) curve analysis to account for such differences in our meta-analysis.[28, 29] We also used a generalized linear mixed model to evaluate differences in diagnostic accuracy between patient groups or methods. For all of our statistical analyses, we used R 2.6.0.[30]

**Results**

**Patient characteristics**

The characteristics of all 326 patients in our single-institution study are summarized in Table 1. All patients were female (mean age at diagnosis, 55.7 years [range 23.5-88.5]). The mean tumor size was 14.9 mm (range, 1.0 to 82 mm). SSL identified the SLNs in all patients. The mean number of SLNs removed was 3.2 nodes per patient.

**SLN Findings, by Method and Tumor Size**

Of the 326 patients who underwent IFS of SLNs, 99 (30.4%) had positive SLNs diagnosed by permanent-section pathologic analysis (PSPA). Of those 99 patients, 39 (39.4%) had negative results according to the IFS. IFS yielded a sensitivity of 60.6%, a specificity of 100%, and an accuracy of 88%. The positive predictive value was 100% and the negative predictive value was 83.2%. We found no false-positive IFS.

**MAM vs. Mi/ITC**

Of the 99 SLN-positive patients, 61.6% had MAM (Table 2) and 38.4% had Mi/ITC (Table 3). The sensitivity of IFS was significantly lower in the Mi/ITC group (28.9%) than in the MAM group (80.3%) ($p<0.0001$). Sensitivity was not significantly correlated with tumor size in either the MAM group ($p = 0.22$) or the Mi/ITC group ($p = 0.74$).

In the Mi/ITC group, 13 (34.2%) patients were found to have metastasis in SLNs when PSPA was done using H&E staining; 12 (31.6%), using IHC. The Mantel-Haenszel statistical method to control for tumor size showed a significant difference in the sensitivity of IFS between the MAM group and the Mi/ITC group ($p < 0.00001$). In the Mi/ITC group, 8 patients had only ITC deposits in SLNs; the sensitivity was 0% (0/8) in these patients.

**Meta-analysis**

A total of 47 articles (including our own data) reported sufficient data for cross-tabulation of the results of IFS of SLNs against PSPA.[31-76] Of these articles, 2 evaluated metastasis in frozen section SLNs using H&E staining and ultra-rapid cytokeratin IHC.[36, 37] In those 2 studies, we included only the results of H&E staining, since few patients underwent ultra-rapid IHC. Most of the IFS SLNs were stained by H&E or toluidine blue. One study reported 2 methods of intraoperative evaluation of SLNs.[41] Results of the 47 studies in our meta-analysis are summarized in Table 2.

The total number of enrolled patients in the 47 studies was 13,062; 32% had positive SLNs and 68% had negative SLNs. When we combined the data from all 47 studies in our meta-analysis of 13,062 patients, the overall sensitivity was 68%; and accuracy, 90%.

Only 18 studies reported comparing the value of IFS for patients with MAM and Mi (Table 3). The false-negative rates in those 18 studies ranged from 0% to 20% for MAM patients and from 0% to 89% for Mi patients. Of the studies, only 5 reported the results of IFS of ITC deposits (Table 4); 3 of them reported 0% sensitivity for detecting ITC deposits.[31, 37, 70]

Per our meta-analysis, the mean sensitivity for detecting metastasis via the SROC model was 73%; the mean specificity, 100%. The mean sensitivity for detecting Mi, however, was substantially lower: 40%. The mean sensitivity for detecting MAM was 94%. The mean specificity was 99%, regardless of the type of metastasis size. Frozen section was significantly more sensitive for MAM than for Mi in our meta-analysis ($p<0.0001$).

We also analyzed the sectioning and staining methods of IFS and of PSPA. For the different intraoperative sectioning methods, we found no significant differences in diagnostic accuracy measured by SROC curves (data not shown). In contrast, for the different PSPA staining methods, we found the method of combination of H&E and IHC provides the best diagnostic accuracy as measured by the SROC curves ($p < 0.004$).

**Discussion**

Although an accurate method for analyzing SLNs intraoperatively is needed to prevent a second operation for completion ALND for breast cancer patients with node-positive disease, no universally agreed-on method exists. Many surgeons use IFS, however, its use is controversial because its sensitivity varies widely, as our study demonstrates.

In addition to its low sensitivity for detecting Mi/ITC, IFS has other potential disadvantages, including tissue

consumption, artifacts from freezing and thawing of specimens[77-79], increased surgical time and cost. The benefit of avoiding a second surgical procedure must be weighed against the risk of obtaining a false-negative result, which could increase the risk of inaccurate nodal status and stage migration.

If intraoperative imprint cytology (IC) shows negative results, PSPA could still show an accurate positive result, because no specimen loss is involved. In contrast, if IFS shows negative results, the part of the node harboring small metastases could have been lost, so Mi in particular could go unidentified.[38, 77, 78, 80]

To minimize the false-positive rate and to avoid unnecessary ALND, Wada et al.[81] suggested that indeterminate results by IFS must be considered negative at the time of surgery, absent unequivocal evidence of carcinoma. False-positive results in our meta-analysis were rare; however, our meta-analysis suggested that, with IFS, about 1% of patients could potentially undergo an unnecessary ALND.

Recently, a commercially available real-time reverse-transcription PCR assay (GeneSearch BLN assay, Veridex LLC, Warren, NJ) was used to detect SLN metastasis. Viale et al.[82] compared the results of the BLN assay with those of serial IFS in a series of 293 SLNs from breast cancer patients. The BLN assay correctly identified 51 of 52 SLNs with MAM and 5 of 20 with Mi; the sensitivity was 98.1% for detecting MAM; 94.7%, > 1 mm; and 77.8%, > 0.2 mm. Viale et al.[82]concluded that the sensitivity of the BLN assay was comparable to that of histopathologic examination of the entire SLN by serial sectioning at 1.5 to 2 mm. As compared with IFS, the BLN assay for intraoperative SLN analysis yielded better results than those of our single-institution study and our meta-analysis.

The value of IC for intraoperative analysis of SLNs is controversial. A meta-analysis of 31 studies evaluating intraoperative IC for SLNs by Tew et al.[83] found that pooled sensitivity of IC was 63%; specificity, 99%. Pooled sensitivity for macrometastases was 81%; micrometastases, 22%. They concluded that IC is simple and rapid, with good sensitivity for macrometastases but not micrometastases. The sensitivity of frozen section for detecting MAM (94%) and for Mi (40%) in our meta-analysis was better than published reports of IC.[35, 83, 84]

We found that IFS is reliable for detecting MAM and can help avoid reoperations in breast cancer patients, but typically fails to detect Mi/ITC. Multiple published studies also showed that IFS fails to detect Mi/ITC.[40, 46, 47, 55]

However, tissue loss is still a potential concern. It has been estimated that up to 50% of lymph node tissue is lost in the process of “facing up” a frozen tissue block for sectioning during IFS [38], because rapid freezing of the embedding medium makes optimal orientation of the nodal tissue in the block much more difficult than in paraffin

embedding for permanent sections. This phenomenon of tissue loss is well known to practicing pathologists. Given that even small metastatic deposits in the range traditionally regarded as micrometastases (<2 mm) have been proven in large prospective studies to be an independent poor prognostic factor linked with decreased disease-free survival[85], loss of significant amounts of SLN tissue should be avoided if possible. Of note, it is impossible to determine with any accuracy the number of false negative results due to tissue loss from frozen section. The common use of the terminology false negative rate implies a difference between IFS and PSPA since tissue loss cannot be exactly measured in IFS.

Although it is impossible to determine how many patients have been understaged due to tissue loss during IFS of SLN specimens (since the lost tissue is by definition never analyzed), studies that have carefully and exhaustively sampled SLNs through multiple deeper level sections have found that metastatic deposits continue to be found throughout the node.[86, 87] This tissue loss is one of the factors cited by various authors who argue against routine IFS analysis of SLNs.[77, 78]

This has led some authors to contend that grossly benign, diminutive SLNs should be sent for PSPA without IFS evaluation.[79] In contrast, other pathologists would answer the above theoretical concerns regarding tissue loss as a source of false negative results by suggesting instead that pathologists examine technical variables as a source of false negative results. For example, does the pathologist emphasize preserving tissue for PSPA, or do they emphasize rendering a definitive diagnosis on IFS by performing multiple levels of IFS? Also, worthy of note, is that the expertise of the individual performing the sectioning of tissue varies significantly (from skilled technician to resident in some teaching institutions) which leads to a variable amount of tissue lost to the bottom of the cryostat, as does the variability of fatty tissue present within and around lymph node(s), which creates challenges in achieving suitable sections. An important limitation of both our study and our meta-analysis was the lack of any standard for defining clinically suspicious nodes in need of IFS. Specht et al.[88] defined clinically suspicious nodes as firm, shotty, and more prominent than nodes on the contralateral side. This lack of a standard definition of clinically suspicious nodes, in addition to different pathologic techniques and variable institutional experience, may in part explain the wide range of sensitivity reported for IFS.

In conclusion, IFS evaluation may be advantageous at times but has key limitations that must be kept it mind, such as low sensitivity for Mi/ITC and the theoretical potential for tissue loss resulting in a false negative SLN. IFS is

readily performed by most pathologists, without extra equipment or specialized training in cytopathology. Our meta-analysis demonstrates that, although results vary between institutions, overall the accuracy and sensitivity of IFS of SLNs for MAM are excellent at 94%; however, the validity of this technique for detecting Mi/ITC is questionable. No intraoperative method of SLN analysis is considered sensitive enough to rule out Mi/ITC. IFS appears to help avoid secondary operations, at least for most breast cancer patients with identifiable positive SLNs and unequivocal evidence of positive nodal disease.

However, recently the American College of Surgeons Clinical Oncology Group (ACOSOG) Z0011 reported no benefit for ALND for women with clinically node negative breast cancer who have a positive SLN.[89] Our meta-analysis validated the routine clinical use of IFS of SLNs, however, we recognize that the routine use of IFS may soon fall out of favor given the findings of the ACOSOG Z0011 trial[89], which argued against completion ALND for the very patients in whom IFS previously played an important role in the clinical algorithm at many institutions.

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**Table 1. Patient Characteristics (n = 326)**

| Variable | | Number (%) |
|---|---|---|
| Tumor (T) stage | | |
| | T1a | 31 (9.5) |
| | T1b | 83 (25.5) |
| | T1c | 151 (46.3) |
| | T2 | 57 (17.5) |
| | T3 | 4 (1.2) |
| Histological findings | | |
| | Invasive ductal carcinoma | 278 (85.3) |
| | Invasive lobular carcinoma | 29 (8.9) |
| | Other* | 19 (5.8) |
| Surgery | | |
| | Mastectomy | 85 (26.1) |
| | Lumpectomy | 241 (73.9) |

*10 tubular, 5 mucinous, 3 micropapillary, 1 medullary carcinoma