



# Intraoperative sentinel lymph node evaluation: Optimizing surgical pathology practices in an era of changing clinical management

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## ABSTRACT

Axillary lymph node status is an independent prognostic indicator in breast cancer. Intraoperative identification of metastatic carcinoma in sentinel lymph nodes may allow for concurrent axillary lymph node dissection at the time of primary tumor excision. A retrospective review of patients undergoing primary breast cancer excision with sentinel lymph node sampling was performed. Sensitivity and specificity of imprint cytology (touch prep) with and without the incorporation of gross evaluation was determined using permanent section results as the gold standard. Five hundred sixteen lymph nodes were analyzed by imprint cytology in 213 patients, and 203 lymph nodes were analyzed in 74 patients incorporating gross examination. Sensitivity and specificity for the detection of macrometastases by touch prep alone were 60% and 99% respectively with 4 patients undergoing same-day axillary dissection for only micrometastatic disease. False negative causes included lack of transfer of malignant cells in 8 cases and misinterpretation of tumor cells in 6 cases. Incorporating gross examination in the modified protocol resulted in reduced sensitivity of 38%, but achieved the desired 100% specificity and positive predictive value. Imprint cytology alone did not reliably distinguish between micro- and macrometastatic disease. Gross assessment combined with imprint cytology allows for improved assessment of volume of axillary disease, but is an insensitive technique.

## 1. Introduction

Axillary lymph node status is an independent prognostic indicator in breast cancer. In patients with a clinically negative axilla, intraoperative identification of macrometastatic carcinoma (> 2 mm tumor deposit) in sentinel lymph nodes allows for concurrent axillary lymph node dissection (ALND) and complete pathologic staging at the time of primary tumor excision. However, ALND may be associated with morbidity including pain, nerve damage, loss of mobility, lymphedema and, per the American College of Surgeons Oncology Group (ACOSOG) Z0011 clinical trial and the International Breast Cancer Study Group 23-01 clinical trial, has not been shown to improve overall survival in selected groups of women with isolated metastatic disease [1]. Guidelines released by the American Society of Clinical Oncology (ASCO) state that ALND can be avoided in women undergoing breast conserving surgery if sentinel lymph nodes are negative for carcinoma, contain only isolated tumor cells (up to 200 tumor cells and or < 0.2 mm deposit), or contain a micrometastasis (tumor deposit of  $\geq$  0.2 to < 2 mm) [2]. Although intraoperative diagnoses of macrometastatic

involvement may decrease the number of additional, separate operative procedures, there is the potential for diagnostic error. Given the recent guideline changes for surgical management of the axilla, pathology laboratories need to adapt their practices to meet the changing needs of patients undergoing intraoperative axillary lymph node evaluation.

There are multiple potential methods of intraoperative lymph node evaluation, including gross evaluation, imprint cytology (touch preparation), and frozen section. Intraoperative lymph node evaluation by imprint cytology maintains cytologic detail, preserves all diagnostic tissue for permanent section analysis, and allows faster intraoperative preparation of slides while showing comparable sensitivity to frozen section analysis [3]. Imprint cytology has been shown to have high specificity in intraoperative margin assessment of breast tissue and in identifying axillary lymph node metastases [4,5]. However, the impact of cytologic assessment of sentinel lymph nodes on further axillary surgical management has not been fully explored in the context of changing surgical management of the axilla.

To evaluate the performance characteristics of imprint cytology, we performed a retrospective review of patients who underwent

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intraoperative sentinel lymph node evaluation by imprint cytology at the time of primary breast cancer excision at a single tertiary academic medical center. We then introduced a modified intraoperative protocol incorporating both gross assessment and imprint cytology to analyze the effect on distinguishing micro- from macrometastases. Sensitivity and specificity, as well as clinical impact of intraoperative lymph node evaluation by imprint cytology were determined using the modified protocol and compared to the standard protocol.

## 2. Materials and methods

Following Vanderbilt University Institutional Review Board approval, a retrospective review of the surgical pathology database (Cerner Copath, Kansas City, MO) was performed to identify consecutive surgical cases for excision of breast carcinoma with sentinel lymph node evaluation over a 24 month period. Intraoperative assessment for this cohort was performed by sectioning all submitted lymph nodes at 2 mm intervals and performing imprint cytology on one side of each 2 mm slice. One touchprep was performed on each slice, and the resulting slides were stained with hematoxylin and eosin (H&E). Three diagnostic categories were used under this standard protocol: 1) “negative,” 2) “atypical,” or 3) “positive.” All intraoperative cases were interpreted by a surgical pathology fellow with confirmation by an attending surgical pathologist as needed.

A modified protocol was introduced in July 2014 under which all sentinel lymph nodes were sectioned at 2 mm intervals, grossly examined for the presence of suspicious lesions by visual inspection and palpation, and imprint cytology was performed. This protocol contained four diagnostic categories: 1) “negative for carcinoma” if no tumor cells were present on touch prep regardless of gross findings, 2) “atypical cells, not diagnostic of carcinoma” if atypical cells were seen on touch prep regardless of gross findings, 3) “tumor cells present but no definitive macrometastatic disease” if tumor cells were present on touch prep without gross features of macrometastasis, and 4) “tumor cells consistent with macrometastatic carcinoma” if tumor cells were identified on touch prep and gross features of macrometastasis were present. A database search was performed to identify surgical cases for excision of breast carcinoma with sentinel lymph node evaluation using this modified protocol over a 12 month period.

Clinical and pathologic data including patient age, tumor size, histologic type, lymph node status, type of surgery performed and decision to perform same-day ALND were collected for both cohorts. Patients who received neoadjuvant therapy or had a non-epithelial breast malignancy were excluded from the analysis. Resource utilization was analyzed using average intraoperative turn-around time.

## 3. Results

Sentinel lymph nodes from 602 patients were excised during the entire 3 year study period, of which 287 patients received intraoperative assessment of the nodes. Five hundred sixteen lymph nodes were analyzed in 213 patients under the standard protocol, and 203 lymph nodes were analyzed in 74 patients using the modified protocol. Patient characteristics for both cohorts were not statistically different (Table 1). Although lymph nodes were evaluated more frequently in patients undergoing mastectomy, there was no statistical difference in the rate of lymph node micrometastases ( $p = 0.99$ ) or macrometastasis ( $p = 0.84$ ) between the two groups.

Though the absolute number of patients with macrometastatic disease were low (12 patients/year under the standard protocol and 8 patients/year under the modified protocol), macrometastases were missed by both methods (Table 2). Sources of error included lack of transfer of malignant cells in 8 cases and misinterpretation of tumor cells in 6 cases, 4 of which were invasive lobular carcinomas or carcinoma with lobular features (Table 3). Examples of intraoperative and permanent section correlates for different tumor morphologies are

**Table 1**  
Patient demographics and pathologic findings.

	Standard protocol (n = 213)	Modified Protocol (n = 74)	P values
Age (years)			0.78
Range	27–80	34–81	
Mean	57.0	56.6	
Surgery performed			0.74
Mastectomy	171 (80.3%)	61 (82.4%)	
Partial/excision	42 (19.7%)	13 (17.6%)	
Tumor type			0.41
DCIS <sup>a</sup>	48 (22.5%)	13 (17.6%)	
Invasive carcinoma	165 (77.5%)	61 (82.4%)	
Completion dissection			0.79
Same-day	15 (7%)	4 (5.4%)	
Second surgery	6 (2.8%)		0.70
Number of lymph nodes examined	516 (2.4 per patient)	203 (2.7 per patient)	
Positive lymph nodes			
Macrometastatic	24 (11.3%)	8 (3.9%)	0.84
Micrometastatic	10 (4.7%)	4 (2.0%)	0.99
Isolated tumor cells	0	2 (1.0%)	0.08

Abbreviations.

<sup>a</sup> DCIS, ductal carcinoma in situ.

**Table 2**  
Comparison of results from intraoperative imprint cytology analysis vs. permanent section.

Intraoperative result	Permanent result			
	Negative	ITCs <sup>a</sup>	Micrometastasis	Macrometastasis
Standard protocol				
Negative (n = 481)	460	0	5	16
Atypical (n = 8)	6	0	2	0
Positive (n = 27)	0	0	3	24
Modified protocol				
Negative (n = 193)	187	1	3	2
Atypical cells (n = 3)	2	0	0	1
Tumor cells present, not grossly positive (n = 4)	0	1	1	2
Tumor cell present, grossly positive (n = 3)	0	0	0	3

Abbreviations.

<sup>a</sup> ITCs, Isolated tumor cells.

shown in Fig. 1.

As expected, incorporating gross examination in the modified protocol resulted in reduced sensitivity for the identification of macrometastases, but achieved the desired 100% specificity and positive predictive value (Table 4). Although no negative lymph nodes were falsely called positive using the standard protocol, touch imprint did not distinguish between micro- and macrometastatic disease. Under the standard protocol, 15 patients underwent same-day ALND, of which, 11 had macrometastatic disease and 4 had only isolated micrometastatic disease. With the modified protocol, all patients undergoing same-day ALND (n = 4), had macrometastases. A second surgery was required for completion ALND in 3 patients/year under both the standard and modified protocols.

Of the patients who underwent same-day ALND under the standard system, 6 patients had additional positive non-sentinel lymph nodes. Of patients who underwent completion ALND at a later date in the standard protocol cohort, only 1 positive non-sentinel lymph node was identified. Under the modified system, of the 4 patients who underwent same-day ALND, only 1 patient had additional positive non-sentinel lymph nodes. Among the patients who underwent later completion

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