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Diagnostic Accuracy of Imprint Cytology in Sentinel Lymph Node Evaluation of Breast Cancer Patients in a Resource-Limited Setting

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Abstract

Background: Sentinel lymph node biopsy is a standard technique for staging of breast node-negative axilla in patients undergoing a mastectomy or breast-conserving surgery. Evidence on touch imprint cytology performance from resource-limited settings, which depends solely on a single technique, is comparatively limited. The study aimed to test the sensitivity, specificity, and accuracy of touch imprint cytology and compare it with final histopathology as a reference standard.

Methods: The study was a retrospective observational study among 88 breast cancer patients who underwent mastectomy or breast-conserving surgery over two years. Following intraoperative imprint cytology of sentinel lymph nodes, results were communicated to the operating surgeon, who then proceeded with definitive surgery, lumpectomy or mastectomy with or without axillary dissection. Excised specimens were subsequently sent for formal histopathological analysis. A set of diagnostic performance indicators, such as sensitivity, specificity, positive predictive value, negative predictive value, and general accuracy, was determined.

Results: The sensitivity and specificity were found to be 93.8% and 75.0%, respectively. The median number of lymph nodes evaluated per case was 3(IQR: 2, range: 1 to 7). The positive and negative predictive values were 45.5% and 98.2%, respectively; overall accuracy was 78.4%, and all estimates were given with 95% confidence limits, highlighting the reliability of the findings.

Conclusions: Touch imprint cytology demonstrated high sensitivity and a clinically meaningful NPV value in this study, supporting its use as a primary intraoperative technique where frozen

sections were unavailable. Nonetheless, false negative results remain a concern, as they can cause under-treatment and require completion of axillary dissection.

Keywords: *Breast cancer; Diagnostic Accuracy; Histopathology; Sentinel lymph node; Touch imprint cytology*

Introduction

Breast cancer ranks second among total cancer cases across the world in 2022, with a total of 2.3 million cases and 666,000 deaths (6.9% of all cancer deaths) [1]. The most common cancer diagnosed in women was breast cancer, with 2,255 new cases, accounting for 18.5 percent of all cancer cases in women in Nepal [2].

The sentinel lymph node (SLN) is the first node in the regional lymphatic area to receive drainage from the tumor site and is most likely to harbor early metastatic spread [3]. One of the most critical prognostic factors in patients with invasive breast carcinoma is assessment of axillary lymph node involvement [4], which has a direct implication for staging and management of the disease [5].

Prompt identification of sentinel node metastases during surgery can inform the surgeon to make a decision on the axillary node dissection (ALND), saving the patient an unnecessary second operation and the economic and psychological costs [6, 7]. Accurate intraoperative evaluation of the sentinel lymph node allows avoiding unnecessary axillary dissection in patients with an uninvolved axilla, sparing them dissection-related morbidities such as restricted shoulder mobility, vascular or motor nerve injury, and lymphedema [4]. Further, for patients with clinically or radiologically suspicious axillary lymph nodes, confirmation of metastasis using fine-needle aspiration cytology or core-needle biopsy is recommended before axillary lymph

node dissection [7]. Various intraoperative tools have been investigated for their diagnostic accuracy in detecting metastatic lymph nodes, ranging from imprint cytology to spectroscopic evaluation [8,9].

The most common and current way of staging breast cancer (BC) patients who underwent a mastectomy is the SLN assessment [10]. Intraoperative SLN status may be determined by several techniques, such as infrared spectroscopy, frozen sections, and touch imprint cytology (TIC). Besides being rapid and technically straightforward, imprint cytology has good cellular detail. The advantage of this type of non-exfoliative cytology over the frozen section analysis is that it does not only preserve tissue but freezing artifact is avoided as well [11].

Nonetheless, TIC is characterized by several drawbacks, such as the absence of a standard mode of operation, undersampling of the nodes, finding lobular carcinoma micrometastases and macro metastases, and a qualified cytopathologist to read the imprints [12]. According to a previously reported study, the use of TIC and subsequent FS of all SLNs significantly improved intraoperative SLN diagnostics, yielding 86.2% sensitivity, 98.9% specificity, and 96% accuracy when analyzing the data per case [13].

Comparable data from resource-limited settings where TIC is the single intraoperative modality remain comparatively sparse. The present study aimed to determine the sensitivity, specificity, and accuracy of touch imprint cytology and to analyze it with histopathological diagnosis as the gold standard.

Methods

Study design and setting. A retrospective observational study was carried out at BPKIHS, Dharan, Nepal, on patients with breast cancer who had undergone mastectomy or breast-

conserving surgery within the past two years, from 2023 to 2025 A.D. All the eligible patients who met the inclusion criteria during the study period were taken into consideration. No formal sample size was calculated. All eligible patients presented during this study period were included. A total of 88 patients were included in this study.

Participants. The study included female patients with histologically verified invasive breast carcinoma with cN0/ycN0, patients who underwent mastectomy/ breast conserving surgery with SLNB, and the intraoperative imprint cytology of all the retrieved SLNBs. In the meantime, previous axillary surgery and missing or incomplete imprint smears or reports were ruled out.

Sentinel node mapping and imprint cytology technique. Sentinel lymph nodes (SLNs) were determined using a dual-tracer technique: either 2 mL of 1% methylene blue mixed with 0.1 mL of fluorescent dye in 4 mL of normal saline or 2.5 mg of indocyanine green diluted in 4 mL of normal saline mixed with 2 mL of 1% methylene blue into the periareolar area. The injection site was massaged for five minutes before axillary dissection. The nodes that had a blue color with blue lymphatic drainage were considered sentinel lymph nodes. These nodes were further sent to intraoperative consultation. The longitudinal axis of the nodes was cut, and the wet surface was rubbed onto a sterile glass slide at a minimum of three times, after which the staining process was done using toluidine blue and rapid Papanicolaou stain. The results of cytological analysis were received between 30 and 45 minutes, of which staining itself required around 10 to 12 minutes. The reporting cytopathologist was blinded to final histopathological results at the time of intraoperative interpretation. All smears were stained by a single experienced cytopathologist, and interobserver variability was not assessed.

Surgical management and histopathology. Following the reporting of imprint cytology results, the biopsy specimen was fixed in 10% formalin, embedded in paraffin, and stained using

hematoxylin and eosin for histopathological examination. Definitive surgery - lumpectomy or mastectomy with or without axillary dissection- was performed, and the specimen was sent to the histopathology labs, following intraoperative reporting of the SLNs. In a small subset of patients, completion axillary lymph node dissection was performed despite a negative sentinel lymph node, based on the operating surgeon's discretion. It was done by an experienced breast surgeon with a standard institutional guideline regarding all breast surgery. In patients with positive sentinel nodes on both imprint cytology and histopathology who underwent axillary dissection, total and non-sentinel positive lymph nodes were additionally assessed.

Neoadjuvant therapy. Patients received neoadjuvant therapy as per standard institutional protocol based on clinical staging and receptor status, and surgery was performed at a standardized interval following completion of the final cycle.

Statistical analysis. Data were entered in Microsoft Excel version 16 and exported to SPSS software (IBM, standard version 25) for analysis. The specificity, sensitivity, diagnostic accuracy, positive predictive value, and negative predictive value of TIC were determined using histopathological diagnosis as the gold standard. Associations between categorical variables were assessed using the chi-square test or Fisher’s exact test where the expected cell count is fewer than 5. Agreement between intraoperative cytology and final histopathology was quantified using Cohen’s kappa coefficient. Ninety-five percent confidence intervals for sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated using the Clopper-Pearson exact method. A p-value less than 0.05 was considered significant.

Result

Table 1 presents the demographic characteristics and corresponding pathological findings. A total of 88 patients participated in the study. Most patients were middle-aged, comprising 60.2% of the cohort and aged 40-60 years. Indocyanine green with methylene blue was used in most cases (59.1%), while a combination of Fluorescence with methylene blue dye was used in only 40.9% of cases. In imprint cytology, 62.5% of the samples were negative, whereas 37.5% were positive. Sentinel lymph node biopsy revealed that 81.8% of cases were negative and 18.2% were positive.

In Table 2, the distribution of patients who received neoadjuvant therapy compared to those who underwent upfront surgery has been presented. The majority of patients proceeded directly to surgery without receiving neoadjuvant treatment. This shows that neoadjuvant therapy was used in 26.1%, indicating it was selectively applied based on clinical indications, whereas upfront surgery remained the predominant management approach in this study population.

The clinicopathological characteristics of the study participants are summarized in Table 3. The median age of the patients was 48.5 years, indicating that most patients were middle-aged adults. A median of three sentinel lymph nodes was submitted for imprint cytology, which reflects standard intraoperative practice. In the final histopathology, more lymph nodes were analyzed per case (median: 10), enabling a more detailed evaluation of nodal status.

Table 4 represents the nodal burden characteristics. Among the 16 patients with a histopathologically confirmed positive sentinel lymph node, the median number of positive sentinel nodes was 1.5 (IQR: 1- 2, range: 1- 3). Ten patients (11.36%) had at least one additional positive non-sentinel lymph node identified on axillary dissection. Among the 15 patients with positive sentinel nodes who underwent axillary dissection, the median total positive lymph nodes

harvested was 2 (IQR 1-3), and the median non-sentinel lymph node was 0 (IQR 0-1). Sixty percent had no further positive nodes on dissection.

Table 5 presents the distribution of imprint cytology results based on the application of neoadjuvant therapy in patients. In the cohort of patients who did not receive neoadjuvant therapy, 38.5% of the patients had positive imprint cytology, which indicated an extra load of nodal metastasis at surgery. Conversely, patients who underwent neoadjuvant therapy had a low rate of imprint positivity (34.8%), which indicated a treatment effect on nodal disease. This disparity, however, failed to be statistically significant ($p = 0.754$), which implies that although something is seen to be decreased with the use of neoadjuvant therapy, the result might be due to chance. Clinically, this trend is consistent with a possible role of neoadjuvant therapy in downstaging axillary disease, though non-significant results in a small subgroup cannot be confirmatory, and larger studies should be conducted to support this effect.

Table 6 illustrates the distribution of the results of the biopsy in patients receiving neoadjuvant therapy and differentiating them through upfront surgery. In non-neoadjuvant therapy patients, 78.5% of the patients had a negative biopsy and 21.5% had a positive biopsy. Among the 23 patients who received neoadjuvant therapy, 21 (91.3%) had a histopathologically negative biopsy, and 2 (8.7)% had a positive result.

The Fisher's exact test ($p = 0.220$) shows that neoadjuvant treatment with a biopsy test was not statistically significant. This indicates that the presence of neoadjuvant therapy did not have a significant effect on the probability of either positive or negative Biopsy among this group of people.

When comparing axillary lymph nodes by imprint cytology and histopathology (Table 7), the results were highly correlated in an analysis of the two techniques. Out of the 33 cases that were positive on the imprint, 15 were found to be positive on histopathology; the remaining 18 were false positives. In 55 imprint-negative cases, there were 54 true negatives and 1 false negative. This was a significant association ($p < 0.001$) with moderate agreement between imprint cytology and histopathology (Cohen's $\kappa = 0.486$). Clinically, imprint cytology is a sound intraoperative approach that identifies the majority of axillary lymph node involvement, reducing unnecessary axillary dissections and their associated morbidity, without compromising diagnostic quality.

In Table 8, a detailed overview reveals the diagnostic effectiveness of imprint cytology in the detection of axillary lymph node metastasis, where the histopathological test is used. The sensitivity and specificity were calculated to be 93.80% and 75%, respectively. The positive predictive value was found to be 45.50%, and the negative predictive value was found to be 98.20%. Overall accuracy in imprint cytology was found to be 78.40%, with all estimates having tight 95% intervals, hence underlining the consistency of imprint cytology to exclude unwarranted axillary lymph node excision.

Discussion

The present study evaluated the effectiveness of intraoperative touch imprint cytology (TIC) in guiding sentinel lymph node (SLN) assessment in patients who are undergoing mastectomy or breast-conserving surgery in a resource-limited environment. The 93.80% sensitivity, 75% specificity, and 78.40% accuracy support the concept that TIC is a useful and applicable intraoperative procedure that can guide surgical decision-making, especially in situations where frozen section facilities are unavailable or too expensive.

The sensitivity of 93.80% obtained in this research is comparable to reported values in the modern literature. Yang et al. meta-analysis of 4,073 patients indicated a weighted sensitivity of 77% of TIC [12], and its pooled sensitivity, as described by Ahuja et.al., of 85.24% between studies discussing TIC versus frozen section [3]. The increased sensitivity shown in the current study could be attributed to the standardized use of a dual-tracer method of SLN location and a median of three nodes being reported per case, which increases the likelihood of sampling the concerned nodes. Conversely, a 12-year single-center study conducted by Bayram et al. on 2,528 patients found a significantly lower sensitivity of 65.8% [14]. This difference is likely due to variation in sample size, learning curves within an institution, and heterogeneity in the included histological subtypes, especially the difficult detection profile of lobular carcinoma. This total accuracy of 78.40% is slightly below the pooled accuracy of 80 to 90 percent in various studies and arguments in favor of TIC as a diagnostically meaningful instrument in the operating room [3, 12].

The specificity used in the current study of 75% is less than the reported specificity of >99% by Chang et al. (4327 cases) [10] and the pooled specificity of 99 by Yang et al.'s meta-analysis [12]. The eighteen false-positive cases in our cohort may be a result of interpretive issues in resource-limited environments, such as the misclassification of benign epithelial inclusions, reactive sinu-histiocytosis, or cells of capsular nevus as malignant deposits - one of the pitfalls of interpreting TICs [11, 12]. Subjective properties of cytological diagnosis, the lack of interobserver validation, and a relatively small sample size might have all led to a decreased specificity. Nevertheless, a 98.20% negative predictive value (NPV) of the outcome represents a clinically significant outcome. The greatest operational usefulness of intraoperative TIC is arguably a high NPV, as it would provide surgeons with adequate cause to prevent axillary

lymph node dissection (ALND) in cases with node-negative disease, and prevent the morbidity of unnecessary dissection with lymphedema and limited shoulder range, which has been well documented [3].

The false negative rate of 6.2% (one case) is less than the reported rate mentioned in the study of 13% as noted by Aldoheyan et al. [4], indicating that the diagnostic reliability of the cohort was satisfactory. False negative in TIC can be explained mainly by micrometastases and isolated tumor cells (ITCs) that may not exfoliate sufficiently during touch preparation and are usually too small to be sampled by the part of the section used for touch [15,16]. In a meta-analysis of sentinel node imprint cytology, Tew et al. showed that TIC sensitivity to micrometastases is significantly less (22%) than for macrometastases (81%) [15] - a result also confirmed by Uno et al., who also found the sensitivity in macrometastases to be 100%, although they admitted that smaller metastases were below detectable diagnosis [17]. All of these data point to the idea that, although TIC is good when it comes to macrometastases, its limitations in micrometastatic disease are intrinsic limitations [17]. Seenu et al. showed that combining TIC with frozen section improved sensitivity to above 93%, reducing false-negative rates when resources are available [18].

Consistent with this, most sentinel node positive cases in this cohort carried a low nodal disease burden, with a median of 1.5 positive sentinel nodes (IQR 1-2, range 1-3), which may partly explain the favorable sensitivity observed, given that touch imprint cytology is known to perform less reliably with low volume or micrometastatic disease [15,17]. Additional non-sentinel nodal disease was identified in 10 patients (11.36%), in whom axillary dissection revealed positive non-sentinel nodes beyond what imprint cytology and the sentinel node itself had shown. This finding does not reflect the limitation of imprint cytology, which evaluates only the sentinel

nodes identified intraoperatively, but highlights that sentinel node status alone does not always capture the full extent of axillary disease.

The high NPV (98.20%) in this study may be attributed to the dual tracer used to identify SLN and the submission of a median of three lymph nodes per case for cytological analysis. The increased tracer uptake and comprehensive lymphatic mapping enhance the yield of SLN and thus the probability of sampling the most diagnostically representative ones [19]. Despite this, the large confidence intervals come with many of the estimates on the statistical ambiguity of small-sample diagnostic research. To reduce these estimates, bigger prospective studies, preferably with a pre-selected sample size, should be conducted to establish the external validity of these results.

In this study, 26.1% of the patients were given neoadjuvant chemotherapy (NAC) before undergoing surgery. The difference did not have statistical significance, but a tendency was noticed toward reduced TIC positivity in the NAC group (34.8%) than in those who underwent upfront surgery (38.5%). Treatment-induced morphological changes in NAC-exposed nodes, including fibrosis, tumor cell degeneration, and reduced cellularity, can complicate cytological interpretation and have been associated with reduced TIC sensitivity in the post-NAC setting [5, 20]. Despite the trend toward lower imprint positivity in our NAC cohort, the non-significant p-value (0.754) and small subgroup size (n=23) prevent any firm conclusions. A significant decrease in TIC sensitivity was reported to be 38.2% in the post-NAC environment by Gimbergues et al. because of morphological changes in both metastatic deposits due to treatment [21]. Equally, Ersoy et al. pointed out that the post-NAC microenvironment represents unique interpretive dilemmas to intraoperative cytology because the treatment effects may either cover up cytological atypia or even show degenerative changes, a phenomenon that mimics benign

outcomes [5]. These findings have significant clinical implications: a negative result of TIC after NAC must not be interpreted without additional implications to rule out residual nodal disease. This limitation should be considered by clinicians, and the institutional protocol might need to take into consideration the post-NAC setting in the application of the TIC-based intraoperative decision algorithm.

In addition to the diagnostic accuracy, TIC also has a number of useful benefits that are especially useful in healthcare settings that are limited in resources. It is considerably quicker than frozen section analysis, including a staining turnaround of about 10 to 12 minutes and a total turnaround of 30-45 minutes, which remains faster than an average of 80 minutes in cryostat-based processes reported by Abe et al. [22], and timely intraoperative decision-making can be carried out without increasing the length of time in the OR.

Being a non-destructive method, TIC retains all the nodal tissue to allow conclusive histopathology processing, a factor that in this case enabled a complete assessment at a median of 10 lymph nodes that were examined on permanent sections. This maintenance of tissue integrity is a cited strength over frozen section, in which loss of tissue due to cryosectioning and freezing artifacts can result in compromised further histological evaluation [3, 6]. Moreover, TIC does not need specific cryostat facilities, trained cryotechnicians, or the related infrastructure, and can be utilized and be cost-effective in environments lacking these facilities. These peculiarities precondition TIC as a pragmatic frontline intraoperative tool in low- and middle-income country (LMIC) environments, in agreement with the conclusions made by Yadav et al.and Ahuja et al [3, 11].

Several limitations should be considered when interpreting these results. The retrospective single-center design prevents generalizability, and a lack of prior calculation of the sample size

decreased the statistical power of subgroup analyses. It did not stratify by tumor subtype, grade, or size of metastasis (micro- versus macrometastasis), which limits knowledge about factors that could predict TIC accuracy. Interobserver variability was also not evaluated because all the smears were examined by a single cytopathologist, and future experiments should involve the use of multipathologists to determine reproducibility. Lastly, there was no co-comparator of routine frozen section in all cases; thus, the formal importance of TIC versus FSB as a diagnostic contributor could not be tested in this cohort.

Conclusions

This research illustrates the good concordance of intraoperative TIC with the final histopathologic assessment of SLN in breast cancer patients who underwent a mastectomy or breast-conserving surgery. The combination of high sensitivity (93.8%), a clinically relevant NPV (98.2%), turnaround time, tissue retention, and minimal infrastructure makes TIC an effective tool, particularly in a resource-constrained environment where frozen section is not routinely accessible, supporting its use as a primary modality in low-resource surgical settings. Prospective, multicenter studies with sufficient sample sizes, stratification of the histological subtype, and interobserver evaluation will be crucial in the future to clearly establish the role of TIC in modern axillary staging algorithms, even under the conditions of the post-NAC setting.

Statement of Ethics

The protocol of this research was reviewed and approved at the Institutional Review Committee of B.P. Koirala Institute of Health Sciences, Dharan, Nepal [Approval number: IRC/3233/025]. All participants were informed and given written consent before being included in the study.

Consent for Publication

Not Applicable

Availability of data and materials

The dataset generated and analyzed during the current study is available from the corresponding author upon reasonable request.

Competing Interests

The authors do not have any competing interests.

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319

320 **Table 1:** Distribution of Demographic and Clinicopathological Characteristics of Study

321 Participants

Variables	Categories	Frequency	Percent (%)
Age group (years)	<40	14	15.9
	40–60	55	62.5
	≥60	19	21.6
Type of dye	ICG + methylene blue	52	59.1
	Fluorescent + methylene blue	36	40.9
Imprint cytology	Negative	55	62.5
	Positive	33	37.5
SLNB	Negative	72	81.8
	Positive	16	18.2

322

323 **Table 2**: Distribution of Patients by Neoadjuvant Therapy Status

Group	Frequency	Percent (%)
Neoadjuvant therapy received	23	26.1
Did not receive neoadjuvant therapy	65	73.8
Total	88	100

324

325 **Table 3**: Clinicopathologist characteristics of study population

Variable	n	Median (IQR)	(Minimum - Maximum)
Age in years	88	48.5 (16)	26–76
Number of nodes sent for imprint	88	3 (2)	1–7
Total nodes examined in Histopathology	88	10 (7)	1–29
Number of positive lymph nodes	19	2 (2)	1-21

326

327 **Table 4**: Sentinel and Non-sentinel Nodal Disease Characteristics

Variable	Result
Number of sentinel lymph nodes examined, median (IQR)	3 (2–4)
Range	1–7
Number of positive sentinel lymph nodes, median (IQR)	1.5 (1–2)
Range	1–3
Number of additional positive non-sentinel lymph nodes, median (IQR)	0 (0–0)

Range	0–20

328

329 **Table 5**: Association between Neoadjuvant Therapy and Intraoperative Imprint Cytology Results

Neoadjuvant Therapy	**Imprint Cytology**		**Total**	**% Positive**	**p-value**
	Negative	**Positive**			
Not received	40	25	65	38.50%	0.754
Received	15	8	23	34.80%	
Total	55	33	88	37.50%	

330

331 **Table 6**: Association Between Neoadjuvant Therapy and Biopsy Result

Neoadjuvant Therapy	**Histopathology**		**Total**	**% Positive**	**p-value**
	Negative	**Positive**			
Not Received	51	14	65	21.50%	0.220
Received	21	2	23	8.70%	
Total	72	16	88	18.20%	

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333 **Table 7:** Association Between Intraoperative Imprint Cytology and SLNB Findings

Imprint	**HPE Result**	**Total**	**p value**

	Positive	Negative		
Positive	15	18	33	<0.001
Negative	1	54	55	
Total	16	72	88	
Cohen's kappa (κ)	0.486			

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335 **Table 8**: Diagnostic Performance of Intraoperative Imprint Cytology Compared with Final

336 Histopathology

Diagnostic test results	Value (%)	95% CI (%)
Sensitivity	93.80%	69.8–99.8
Specificity	75.00%	63.4–84.5
Positive Predictive Value	45.50%	28.1–63.6
Negative Predictive Value	98.20%	90.3–100
Accuracy	78.40%	-

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